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Thiazolo[3,2-a]pyrimidines: synthesis methods and biomedical potential

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A B S T R A C T

Thiazolo[3,2-a]pyrimidines are structural analogues of biogenic purine bases, thus may be considered as potential purine antagonists. The synthesis of these heterocyclic systems attracts significant attention from researchers in the field of organic and medicinal chemistry due to their wide range of biological activities, e.g. anti-inflammatory, antimicrobial, antioxidant, antiviral, and anticancer. The high bioactivity of thiazolo[3,2-a]pyrimidine derivatives stimulates the development of fundamentally new synthesis options, which include modern catalytic, microwave and ultrasonic methods for activating cycloaddition reactions, and the improvement of already known methods. This, in turn, became a strong basis for summarizing and systematizing the existing array of literature sources from 2000 to 2024 relating to the methods of obtaining and biomedical profile of thiazolo[3,2-a]pyrimidines and their hydrogenated analogues.

1. Introduction

Thiazolo[3,2-*a*]pyrimidines belong to the privileged azole-azine systems which have attracted increased attention from researchers due to their powerful biomedical potential. The importance of the thiazolopyrimidine nucleus as a molecular platform for the design of bioactive molecules is confirmed by the creation of the antidepressants ritanserin (**I**) and setoperone (**II**) based on it (**Fig. 1**).[1] In addition, thiazolo[3,2-*a*]pyrimidine derivatives have found practical application as enantioselective organocatalysts in acylation reactions[2] and catalysts for homo- and copolymerization[3].

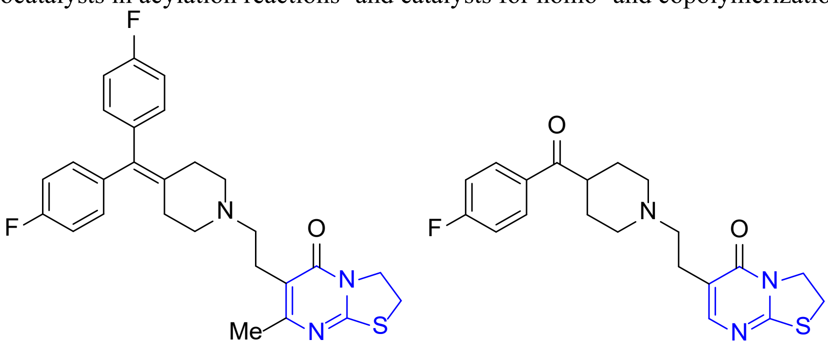

Fig. 1. Ritanserin (**I**) and setoperone (**II**) drugs.

The design and directed synthesis of thiazolo[3,2-*a*]pyrimidines and their condensed analogues is a relevant area of modern heterocycle chemistry, as confirmed by a number of review papers published over the last 10 years.[4–8] Recent advances in the development of potential anticancer agents in the thiazolopyrimidine family are summarized in a 2022

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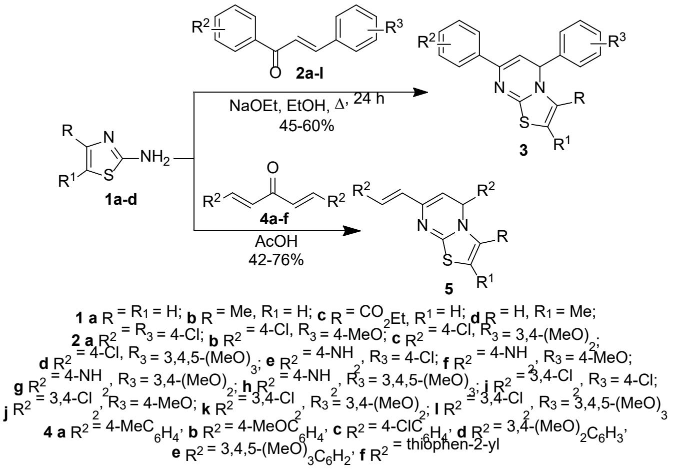
review.[9] It is worth noting that the presented publications analyzed and systematized a large amount of literature data that relate exclusively to polycyclic systems with a thiazolopyridine fragment. However, there have been no attempts to summarize the literature highlighting the synthetic and biomedical potential of the basic thiazolo[3,2-*a*]pyrimidine scaffold. In view of this, it seemed appropriate to analyze and systematize the original articles published over the past 25 years concerning the methods of synthesis and biological action of thiazolo[3,2-*a*]pyrimidines and their hydrogenated analogues.

2. Annelation of the pyrimidine nucleus to the thiazole ring

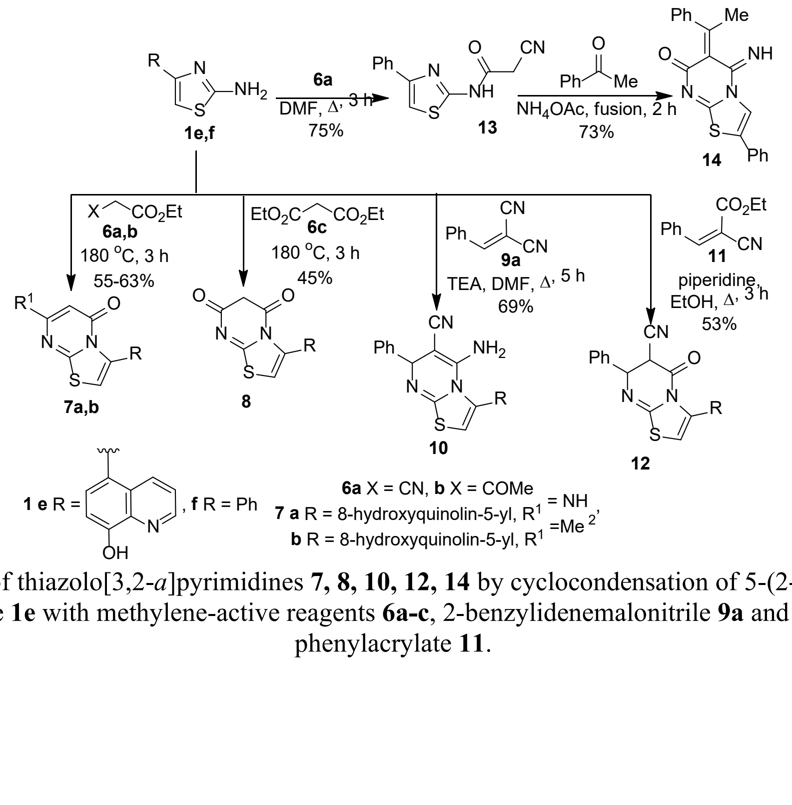
2.1. Cyclocondensations based on 2-aminothiazoles

The most common method for creating combinatorial libraries for medicinal chemistry based on thiazolo[3,2-*a*]pyrimidines is the reaction of 2-aminothiazoles with mono- and dicarbonyl compounds. The synthesis of a series of di- and trisubstituted thiazolo[3,2-*a*]pyrimidines **3** was realized by cyclocondensation of thiazol-2-amines **1a-d** with α,β-unsaturated ketones **2a-l** in alcoholic solution and in the presence of NaOAc.[10] To obtain a series of 7-arylidene-substituted 5*H*-thiazolo[3,2-*a*]pyrimidines **5**, the reaction of 2-aminothiazoles **1a-d** with diarylidene derivatives **4a-f** in AcOH medium proved to be convenient (**Scheme 1**).[11]



Scheme 1. Synthesis of polysubstituted thiazolo[3,2-*a*]pyrimidines **3, 5** by cyclocondensation of 2-aminothiazoles **1a-d** with α,β-unsaturated ketones **2a-l** and diarylidene derivatives **4a-f**.

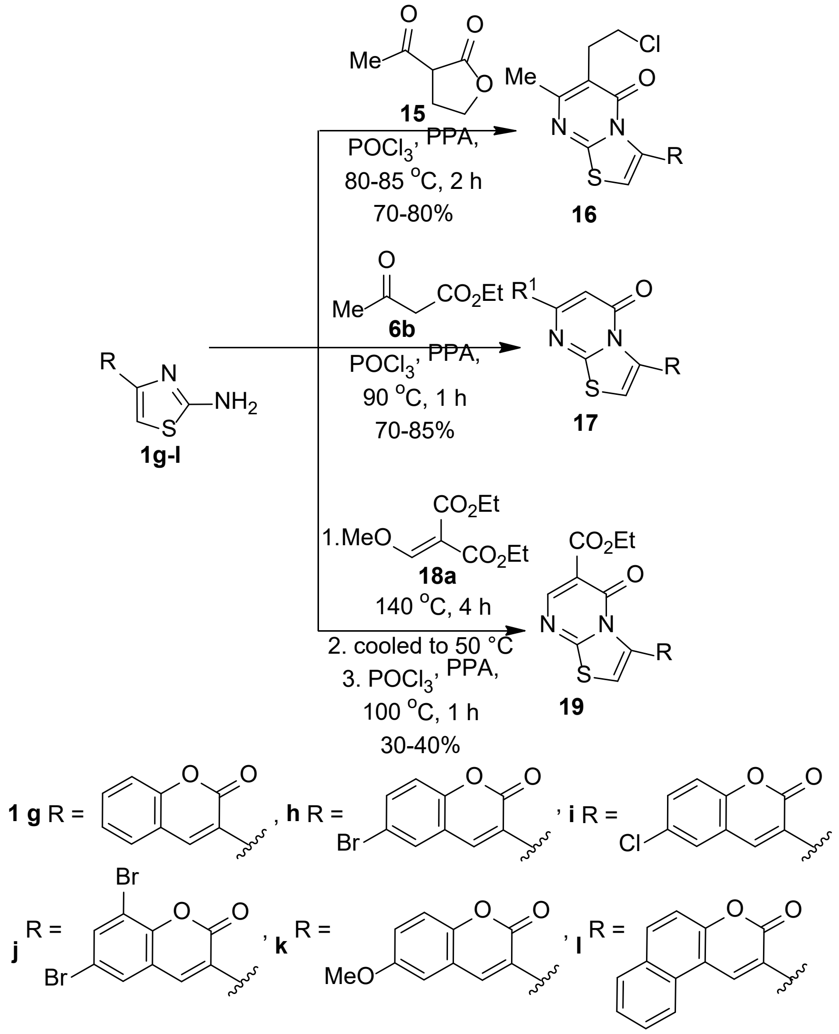
To construct thiazolo[3,2-*a*]pyrimidines **7, 8, 10, 12** containing an 8-hydroxyquinoline fragment, the authors[12] used the cyclocondensation of 5-(2-aminothiazol-4-yl)-8-hydroxyquinoline **1e** with methylene-active reagents **6a-c**, 2-benzylidenemalonitrile **9a**, and ethyl 2-cyano-3-phenylacrylate **11** (**Scheme 2**). Instead, 4-phenylthiazol-2-amine **1f** reacts with ethyl cyanoacetate **6a** in DMF solution to form 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide **13**, which upon fusion with acetophenone in the presence of NH_4OAc produces 6-(1-phenylethylidene)-5*H*-thiazolo[3,2-*a*]pyrimidine **14** (**Scheme 2**).[13]



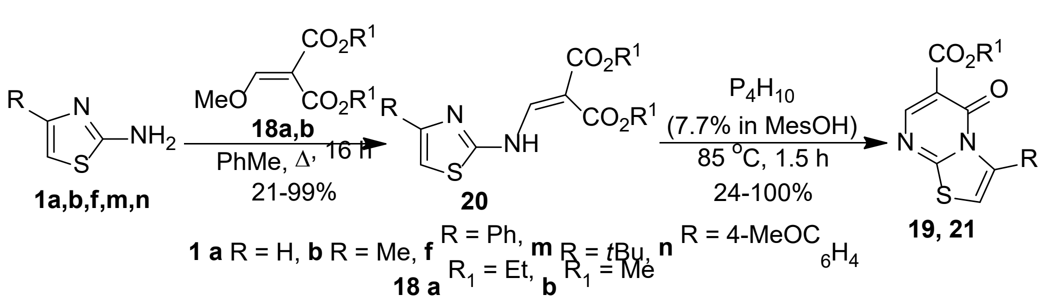
Scheme 2. Synthesis of thiazolo[3,2-*a*]pyrimidines **7, 8, 10, 12, 14** by cyclocondensation of 5-(2-aminothiazol-4-yl)-8-hydroxyquinoline **1e** with methylene-active reagents **6a-c**, 2-benzylidenemalonitrile **9a** and ethyl 2-cyano-3-phenylacrylate **11**.

Condensation of 3-(2-amino-4-thiazolyl)coumarins **1g-k** and the benzannelated analogue **1l** with α-acetyl-γ-butyrolactone **15** in a mixture of polyphosphoric acid (PPA) and $POCl_3$ is a convenient method for the synthesis of 3-substituted 6-(2-chloromethyl)-7-methyl-5*H*-[1,3]-thiazolo[3,2-*a*]pyrimidin-5-ones **16**, and condensation of derivatives **1g-l** with ethyl 3-oxobutanoate **6b** produces 7-methyl-3-(2-oxo-2*H*-chromen-3-yl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-ones **17**. In turn, the reaction of 3-(2-amino-4-thiazolyl)coumarins **1g-k** and diethylmethoxymethylenemalonate **18a** in a PPA/$POCl_3$ mixture yields ethyl 3-(2-oxo-2*H*-chromen-3-yl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one-6-carboxylates **19** (**Scheme 3**).[14]

A two-step method is described in[15] for the synthesis of a series of thiazolo[3,2-*a*]pyrimidinones **19, 21** by the interaction of 2-aminothiazoles **1a,b,f,m,n** with dimethylmethoxymethylenemalonates **18a,b** and subsequent cyclization of the condensation products **20** in the presence of Eaton's reagent (P_4H_{10}/MesOH) (**Scheme 4**).

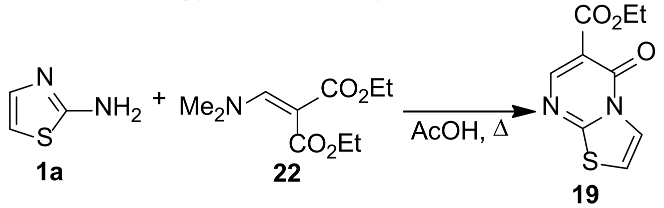


Scheme 3. Synthesis of 3-(2-oxo-2*H*-chromen-3-yl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-ones **16, 17, 19** by condensation of 3-(2-amino-4-thiazolyl)coumarins **1** with α-acetyl-γ-butyrolactone **15**, ethyl 3-oxobutanoate **6b** and diethylmethoxymethylenemalonate **18a** in a PPA/$POCl_3$ mixture.



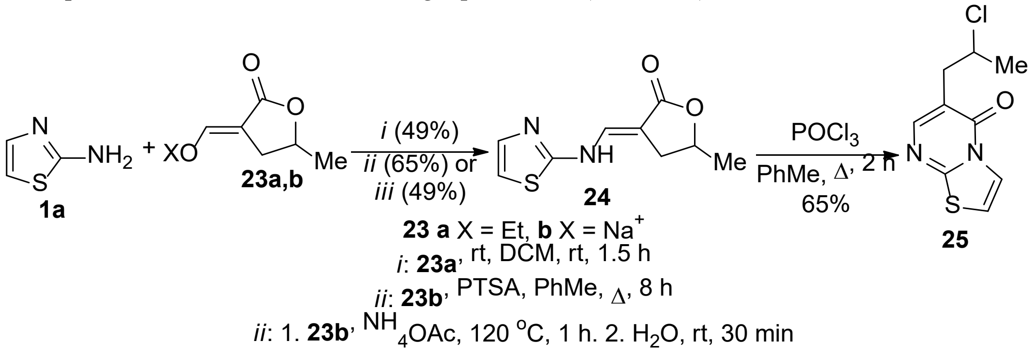
Scheme 4. Two-step synthesis of thiazolo[3,2-*a*]pyrimidinones **19, 21** by the interaction of 2-aminothiazoles **1** with dimethylmethoxymethylenemalonate **18** and subsequent cyclization of the condensation products **20** using Eaton's reagent.

The condensation of thiazol-2-amine **1a** with diethyl 2-[(dimethylamino)methylene]malonate **22** proved successful for the synthesis of ethyl 5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate **19**, (**Scheme 5**).[16]



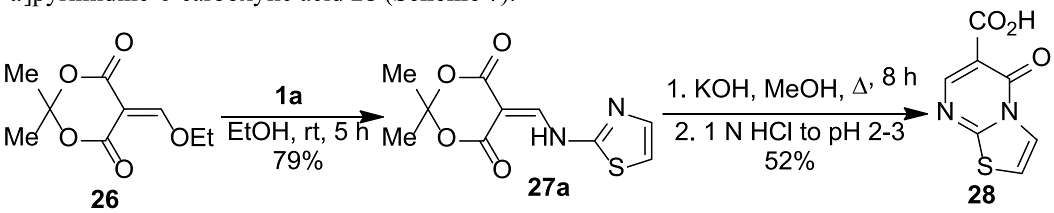
Scheme 5. Synthesis of ethyl 5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate **19** by condensation of thiazol-2-amine **1a** with diethyl 2-[(dimethylamino)methylene]malonate **22**.

An efficient approach to obtain 5*H*-thiazolo[3,2-*a*]pyridin-5-one **25** with a 3-chloropropyl side chain was based on the reaction of 2-aminothiazole **1a** with 3-ylidenefuranones **23a,b** via the step of forming the intermediate enamine **24** which is easily cyclized upon the action of $POCl_3$ to the target product **25** (**Scheme 6**).[17]



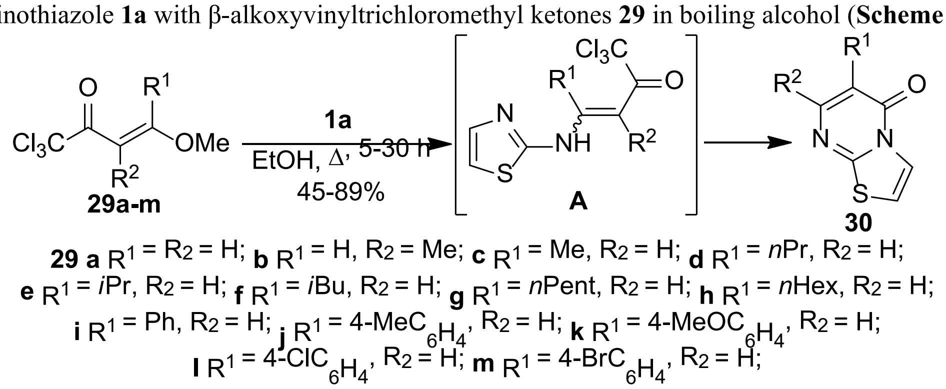
Scheme 6. Synthesis of 5*H*-thiazolo[3,2-*a*]pyridin-5-one **25** by the reaction of 2-aminothiazole **1a** and cyclic β-formyl esters **23**.

Isopropylidene *N*-thiazolaminomethylenemalonate **27a**, obtained by the interaction of 2-aminopyridine **1a** and isopropylidene ethoxymethylenemalonate **26**, turned out to be a convenient substrate for the synthesis of 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid **28** (**Scheme 7**).[18]



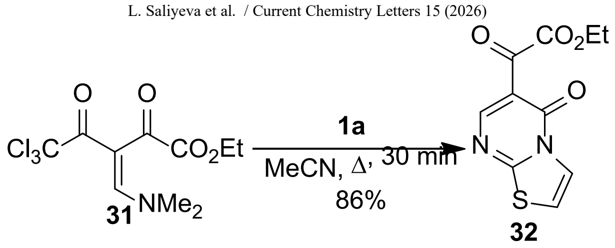
Scheme 7. Synthesis of 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid **28** by intramolecular cyclization of isopropylidene *N*-thiazolaminomethylenemalonate **27a**.

A library of 6-methyl- and 7-alkyl(aryl)-substituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **30** was prepared by the reaction of 2-aminothiazole **1a** with β-alkoxyvinyltrichloromethyl ketones **29** in boiling alcohol (**Scheme 8**).[19]



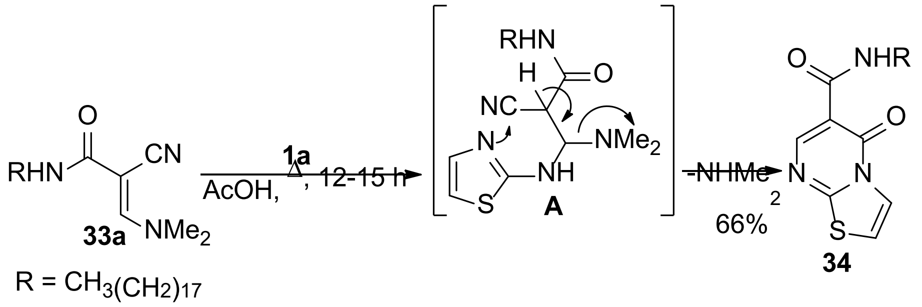
Scheme 8. Synthesis of 6-methyl- and 7-alkyl(aryl)-substituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **30** by the reaction of 2-aminothiazole **1a** with β-alkoxyvinyltrichloromethyl ketones **29**.

The cyclocondensation of thiazol-2-amine **1a** with β-enaminodiketone **31** was used to synthesize glyoxalate-substituted thiazolo[3,2-*a*]pyrimidin-5-one **32** (**Scheme 9**).[20]



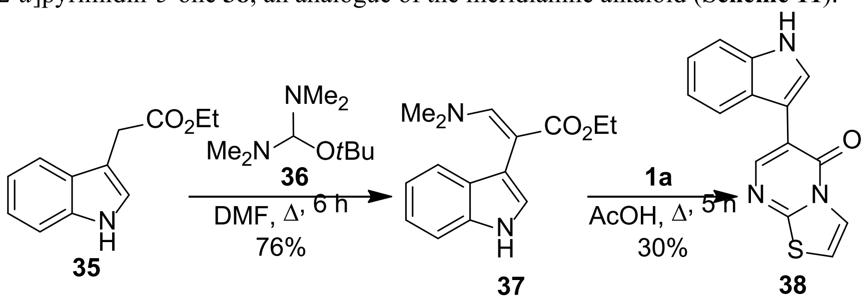
Scheme 9. Synthesis of glyoxalate-substituted thiazolo[3,2-*a*]pyrimidin-5-one **32** by cyclocondensation of thiazol-2-amine **1a** with β-enaminodiketone **31**.

El-Sayed and Katouah[21] successfully used 2-cyano-3-(dimethylamino)-*N*-octadecyl acrylamide **33a** for the synthesis of *N*-alkyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide **34** as a precursor of surface-active biological compounds (**Scheme 10**).



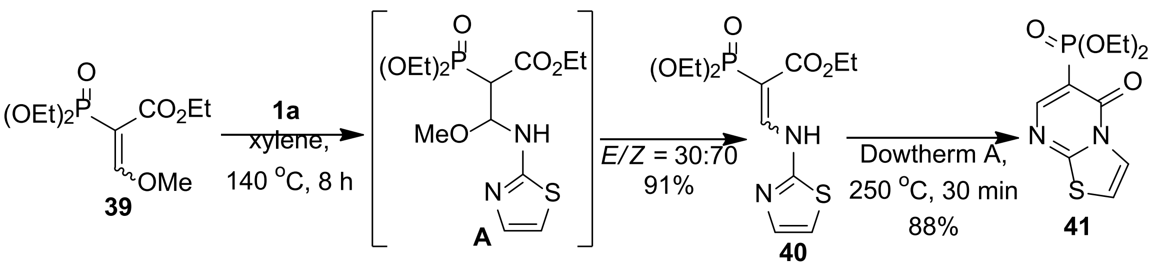
Scheme 10. Synthesis of *N*-alkyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide **34** by condensation of 2-aminothiazole **1a** and 2-cyano-3-(dimethylamino)-*N*-octadecyl acrylamide **33a**.

Ethyl 3-dimethylamino-2-(indol-3-yl)propanoate **37**, prepared from ethyl 3-indole acetate **35** and *tert*-butoxybis(dimethylamino)methane **36** (Bredereck's reagent), upon interaction with 2-aminothiazole **1a** gave 6-(1*H*-indol-3-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **38**, an analogue of the meridianine alkaloid (**Scheme 11**).[22]



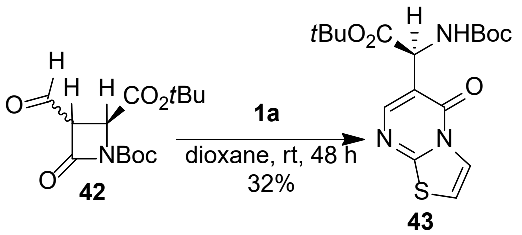
Scheme 11. Synthesis of 6-(1*H*-indol-3-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **38** by the reaction of ethyl 3-dimethylamino-2-(indol-3-yl)propanoate **37** and 2-aminothiazole **1a**.

A simple two-step synthesis of phosphorylated 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **41** was realized from the available 2-diethoxyphosphoryl-3-methoxyacrylate **39** and 2-aminothiazole **1a**. Thermal intramolecular cyclization of the intermediate 3-aminoacrylate **40** proceeded efficiently with complete *N*-regioselectivity and led to the target product **41** (**Scheme 12**).[23]



Scheme 12. Synthesis of phosphorylated 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **41** by the reaction of 2-diethoxyphosphoryl-3-methoxyacrylate **39** and 2-aminothiazole **1a**.

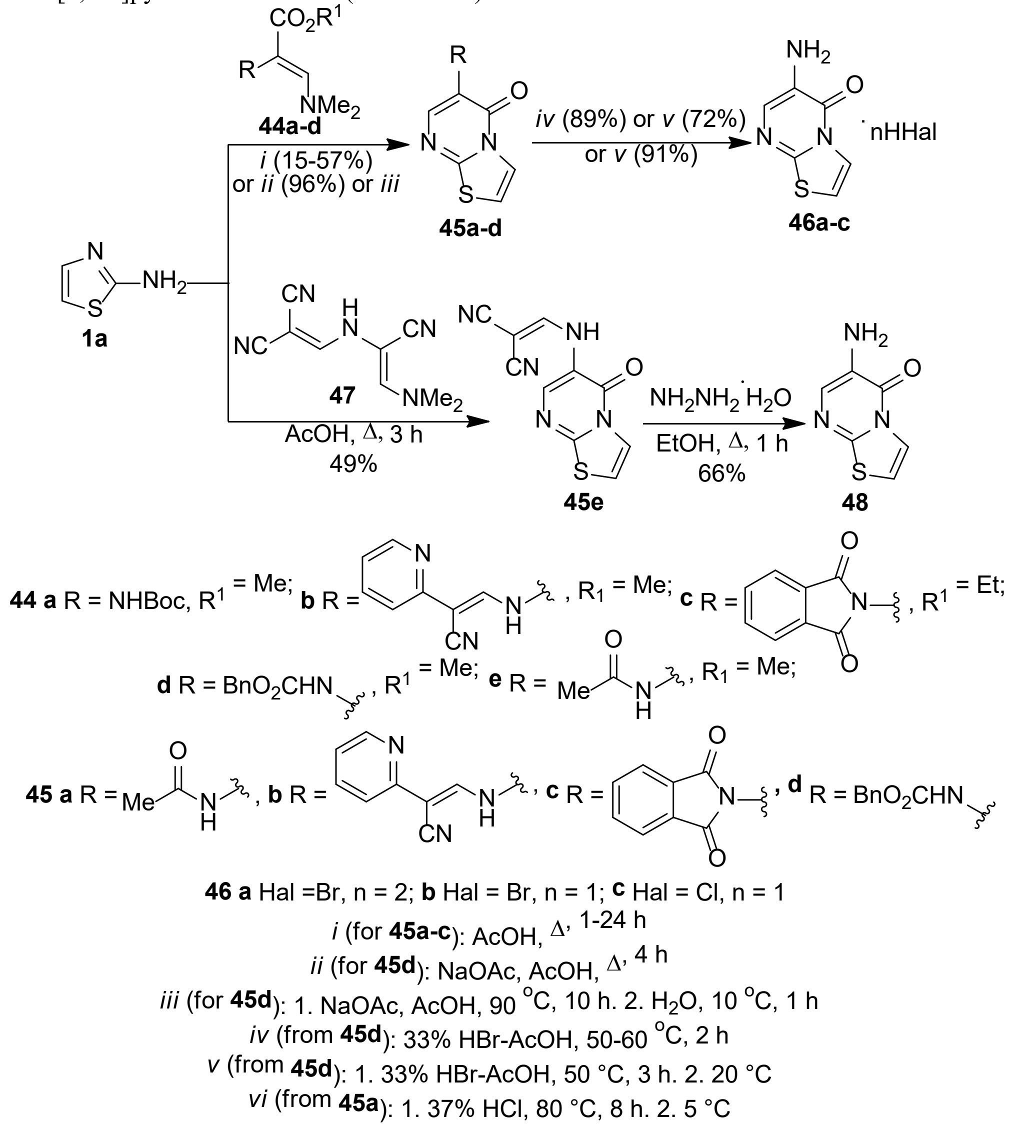
Activated β-lactam aldehyde **42** proved to be an excellent substrate in the ring switching strategy of the preparation of homochiral 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **43** with potential activity towards certain glutamate receptor subtypes (**Scheme 13**).[24,25]



Scheme 13. Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **43** by the ring switching method from β-lactam aldehyde **42**.

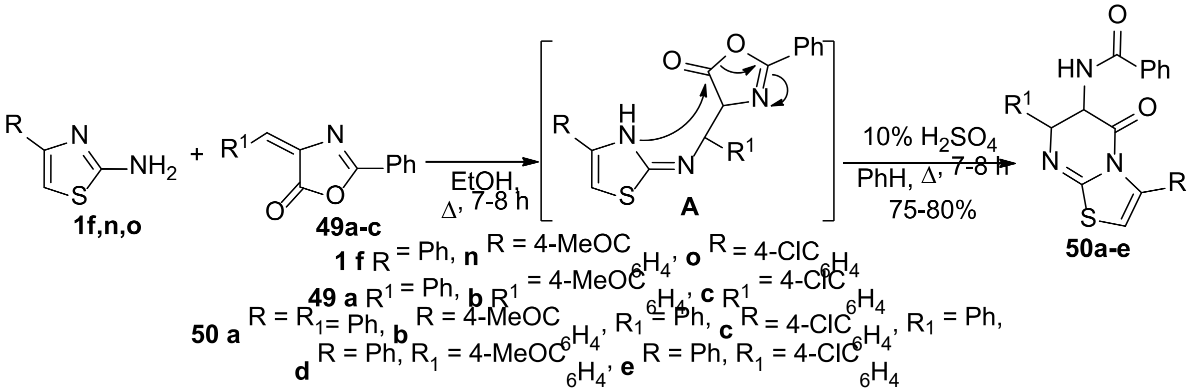
An efficient method for the synthesis of 6-amino-substituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **45** was based on the cyclocondensation of thiazol-2-amine **1a** with propenoates **44** and enamine **47**. It was found that the reaction of propenoates **44a-d** with 2-aminothiazole **1a** proceeds smoothly upon boiling in AcOH[26–28] or in the NaOAc/AcOH system[29] with the formation of the target products **45**, which were converted into the corresponding hydrohalides **46a-d**[29,30] (**Scheme 14**).

In turn, the interaction of 2-aminothiazole **1a** with an equimolar amount of 2,2-dimethylaminoethenyl derivative **47** in boiling AcOH led to 6-ylideneamino derivative **45e**, which upon treatment with hydrazine hydrate in EtOH produced 6-amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **48** (**Scheme 14**).[31]



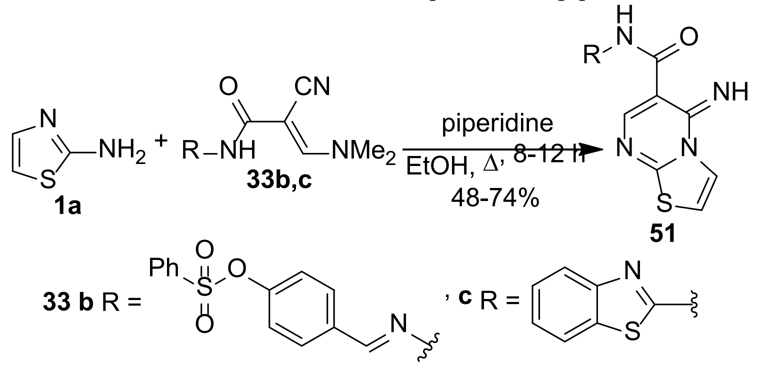
Scheme 14. Synthesis of 6-amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **46, 48** by the interaction of thiazol-2-amine **1a** with propenoates **44** and enamine **47a**.

A two-step synthesis of a series of *N*-(5-oxo-3,7-diaryl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)benzamides **50a-e** was achieved by the reaction of 2-amino-4-arylthiazoles **1f,n,o** with (*E*)-4-arylidene-2-phenyloxazol-5(4*H*)-ones **49a-c** in ethanol followed by intramolecular cyclization of intermediates **A** under the action of catalytic amounts of H_2SO_4 (**Scheme 15**).[32]



Scheme 15. Synthesis of *N*-(5-oxo-3,7-diaryl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)benzamides **50** by the reaction of 2-amino-4-arylthiazoles **1** and (*E*)-4-arylidene-2-phenyloxazol-5(4*H*)-ones **49a-c**.

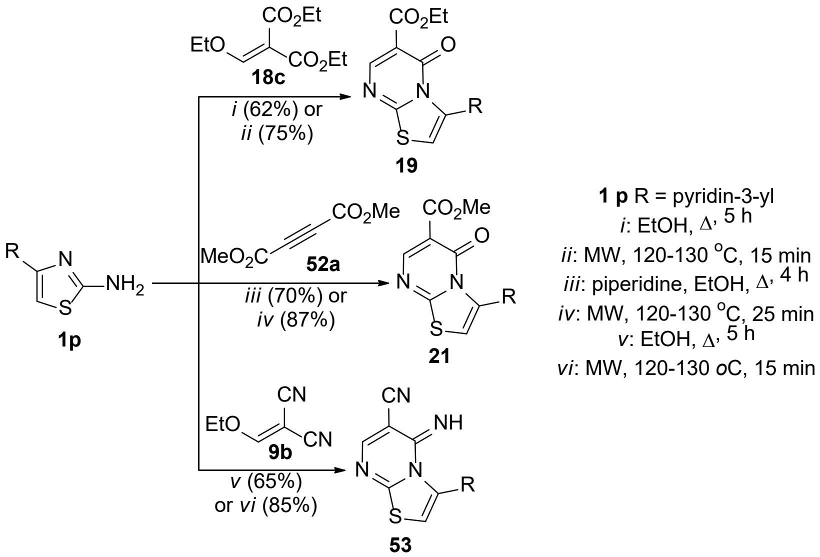
N-Functionalized 5-imino-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamides **51** were obtained by condensation of thiazol-2-amine **1a** and enaminonitriles **33b,c** in alcoholic solution in the presence of piperidine as a base (**Scheme 16**).[33,34]



Scheme 16. Synthesis of 5-imino-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamides **51** by condensation of thiazol-2-amine **1a** and enaminonitriles **33**.

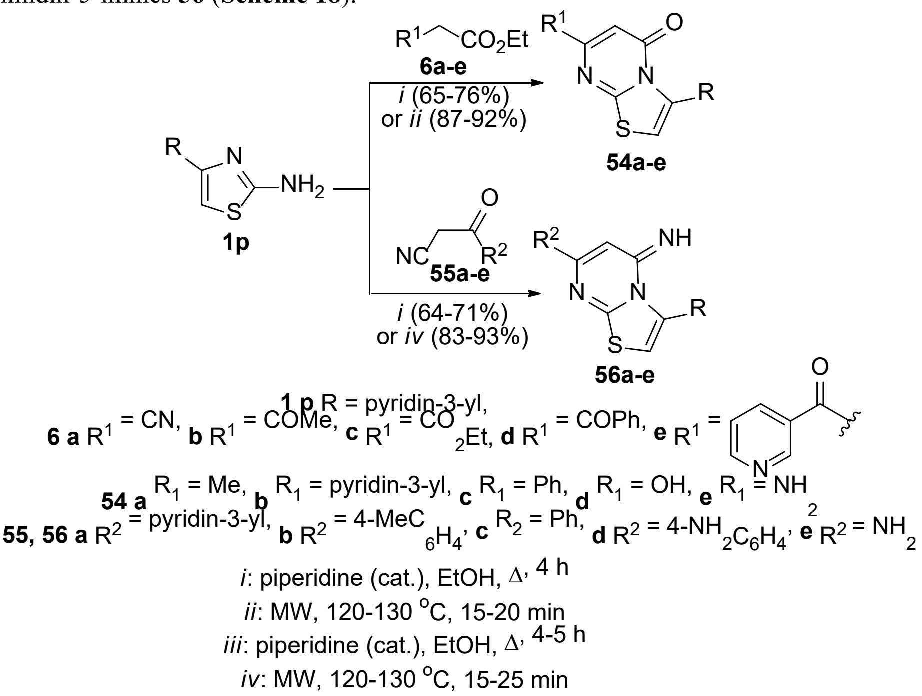
2.2. "Green" methods involving 2-aminothiazoles

A significant part of the literature over the last two decades on methods for constructing the thiazolo[3,2-*a*]pyrimidine nucleus is devoted to green chemistry methods. 5-Oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **19, 21** and 5-imino-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **53** were obtained by cyclocondensation of thiazol-2-amine **1p** with diethyl 2-(ethoxymethylene)malonate **18c**, dimethyl acetylenedicarboxylate **52a** and 2-(ethoxymethylene)malononitrile **9b**, respectively, in boiling alcohol or under microwave irradiation (**Scheme 17**).[35]



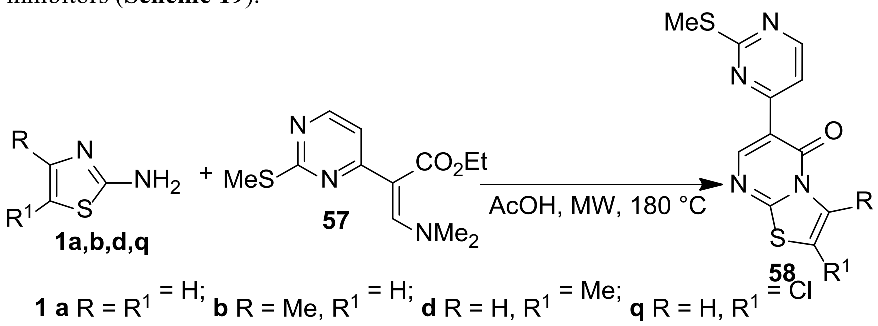
Scheme 17. Microwave synthesis of 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **19, 21** and 5-imino-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **53** by cyclocondensation of thiazol-2-amine **1p** with diethyl 2-(ethoxymethylene)malonate **18c**, dimethyl acetylenedicarboxylate **52a** and 2-(ethoxymethylene)malononitrile **9b**.

Similar reaction conditions were optimal for the creation of a library of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **54** and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-imines **56** (**Scheme 18**).[35]



Scheme 18. Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **54** and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-imines **56** by cyclocondensation of thiazol-2-amines **1** with methylene-active compounds **6, 55** under the action of MW irradiation.

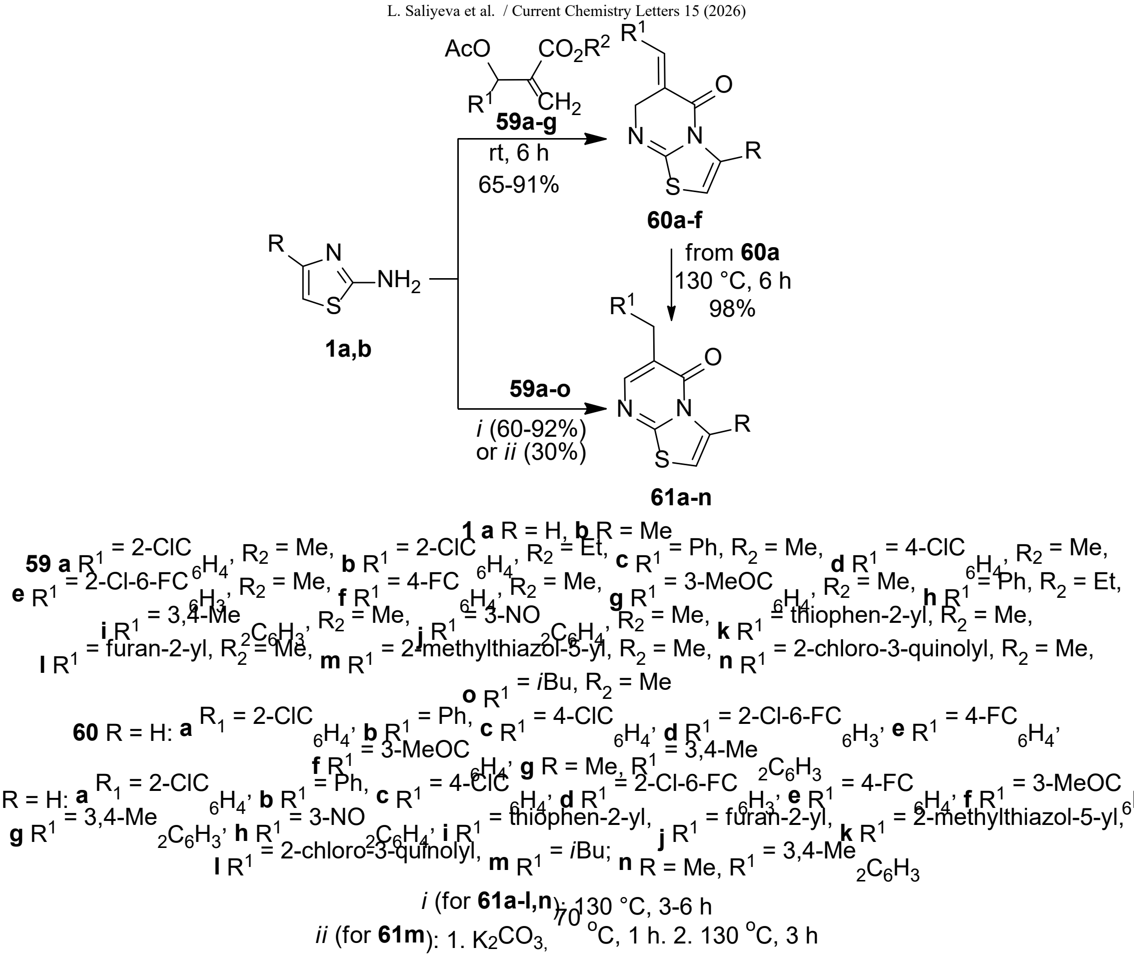
The reaction of 2-aminothiazoles **1** with 2,2-dimethylaminoethenyl derivative **57** under the action of MW irradiation yielded 6-[2-(methylthio)pyrimidin-4-yl]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **58**, key intermediates in the synthesis of acetylcholinesterase inhibitors (**Scheme 19**).[36]



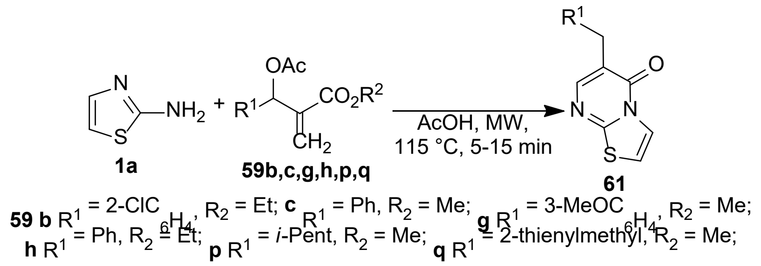
Scheme 19. Synthesis of 6-[2-(methylthio)pyrimidin-4-yl]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **58** by the reaction of 2-aminothiazoles **1** with derivative **57** under MW irradiation.

5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones 61 and the relatively unstable intermediates 6-benzylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 60 were obtained by the reaction of thiazol-2-amines 1a,b with Morita-Baylis-Hillman adducts 59 in high yields in the absence of solvents and bases. It is interesting that thiazol-2-amine 1a with adduct 59i produces 61m rather than the Michael addition product (Scheme 20).[37]

An efficient method for the synthesis of 6-substituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **61** from Morita–Baylis–Hillman adducts **59** was implemented using MW irradiation in acetic acid (**Scheme 21**).[38]

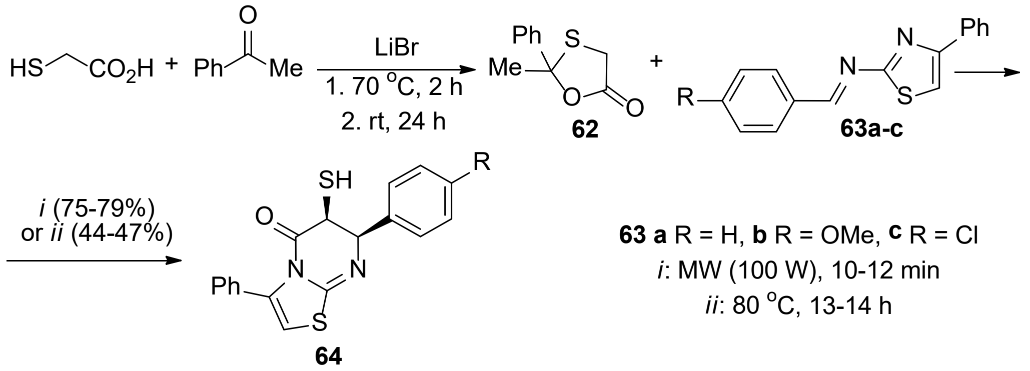


Scheme 20. Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **61** from thiazol-2-amines **1** and acetates of Morita-Baylis-Hillman adducts **59**.



Scheme 21. MW variant of the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **61** by the interaction of thiazol-2-amine **1** with Morita-Baylis-Hillman adducts **59**.

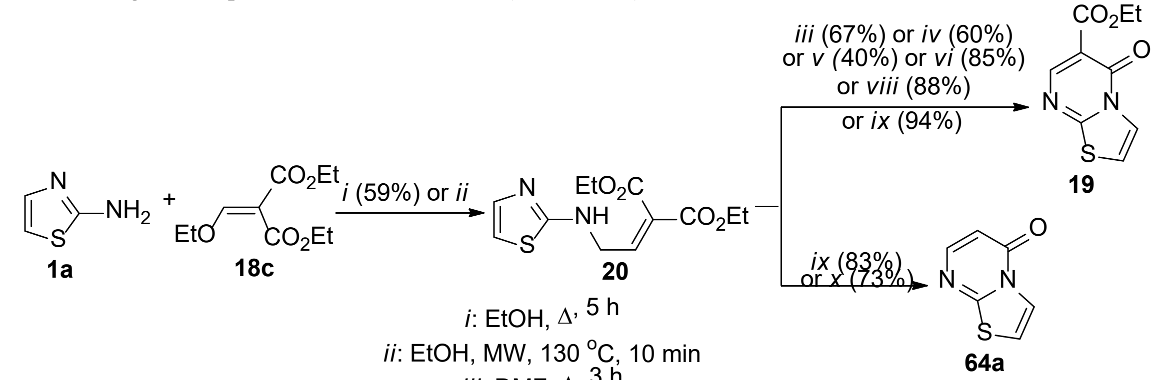
2-Methyl-2-phenyl-1,3-oxathiolan-5-one **62** undergoes stereoselective cyclocondensation with Schiff bases **63** under microwave irradiation or heating without solvent to form 6,7-dihydro-6-mercapto-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **64** (**Scheme 22**).[39]



Scheme 22. Synthesis of 6,7-dihydro-6-mercapto-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **64** by cyclocondensation of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **62** with Schiff bases **63a-c**.

The report[40] describes the synthesis of ethyl 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **19** and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **64** by the Gould-Jacobs reaction using a three-mode pyrolysis reactor. The interaction of 2-aminothiazole **1a** and diethyl 2-(ethoxymethylene)malonate **18b** gave derivative **20**, which, upon heating in DMF solution, under MW irradiation, under flash thermolysis in flow conditions, or under flash vacuum pyrolysis conditions, produced the target **19**. In contrast, the flash thermolysis in flow proved to be effective for the synthesis of thiazolopyrimidinone **64**, (**Scheme 23**).

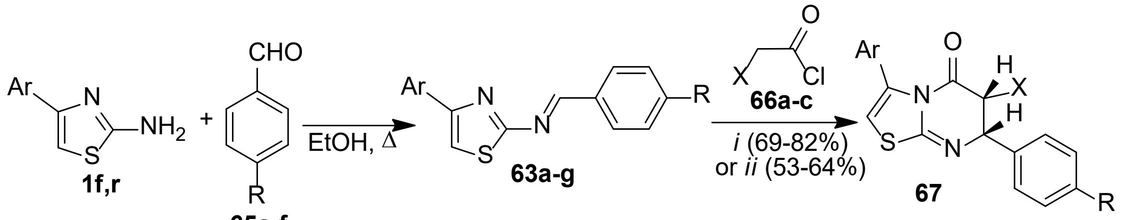
The authors[41] developed a new variant of the Gould-Jacobs reaction in an automated high-temperature and high-pressure flow reactor PhoenixTM, which enabled rapid synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **19** and **64**. Diethyl 2-[2-(thiazol-2-ylamino)ethylidene]malonate **20** obtained by condensation of 2-aminothiazole **1a** with ethoxymethylene compound **18c** was subjected to further thermal cyclization in a PhoenixTM reactor to form 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **19**. The decarboxylated product **64a** was obtained by decreasing the reactant concentration, increasing the exposure time, and increasing the temperature in a flow reactor (**Scheme 23**).



i: EtOH, Δ, 5 h
ii: EtOH, MW, 130 °C, 10 min
iii: DMF, Δ, 3 h
iv: DMF, MW, 150 °C, 30 min
v: DPE, MW, 250 °C, 5 min
vi: flash thermolysis (R_f = 450 °C, P = 80 bar, Fr = 28 mL/min, t = 8.5 s, V = 4 mL)
vii: vacuum flash pyrolysis (T_f = 450 °C, T_i = 140 °C, P = 2.5 ×10^{-1} mbar, t = 30 min, 30 cm × 2 cm)
viii: 390 °C, 4 mL/min, 100 bar, 0.4 M in THF, 0.2 mmol scale
ix: flash thermolysis (R_f = 150 °C, P = 80 bar, Fr = 0.5 mL/min, t = 8 min, V = 4 mL)
x: 390 °C, 0.5 mL/min, 120 bar, 100:1 THF/H_2O (0.05 M), 0.2 mmol scale

Scheme 23. Synthesis of ethyl 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **19** and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **64** by the Gould-Jacobs reaction of 2-aminothiazole **1a** with diethyl 2-(ethoxymethylene)malonate **18b**.

A series of 6-substituted 3,7-diaryl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **67** were synthesized by the [4+2]-cycloaddition reaction of 2-arylideneamino-4-arylthiazoles **63a-g** with monosubstituted ketenes formed in situ from anhydride chlorides **66** under phase transfer catalysis (PTC) conditions in combination with ultrasonic treatment (**Scheme 24**).[42]

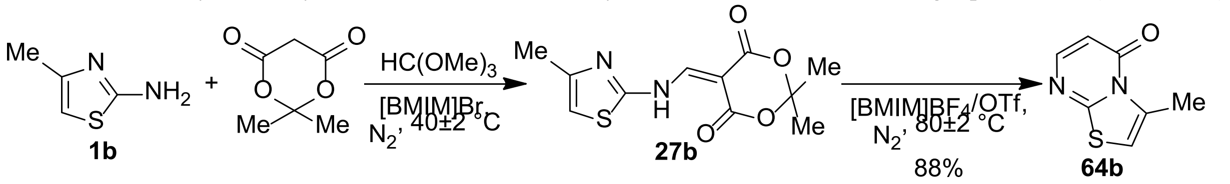


1 f Ar = Ph, **r** Ar = 4-BrC$_6$H$_4$
65 a R = H, **b** R = OMe, **c** R = OH, **d** R = F, **e** R = Cl, **f** R = NO$_2$
63 a Ar = Ph, R = H; **b** Ar = Ph, R = OMe; **c** Ar = Ph, R = Cl; **d** Ar = Ph, R = NO$_2$, **e** Ar = 4-BrC$_6$H$_4$, R = OMe; **f** Ar = 4-BrC$_6$H$_4$, R = F; **g** Ar = 4-BrC$_6$H$_4$, R = OH
66 a X = Ph, **b** X = Cl, **c** X = Br
i: *n*-TBAHSO$_4$, KOH, THF, ultrasonic irradiation, 20-25 °C, 2-3 h
ii: 20-25 °C, 7-9 h

Scheme 24. Synthesis of 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 67 by the [4+2]-cycloaddition reaction of 2-arylideneamino-4-arylthiazoles **63a-g** with monosubstituted ketenes formed in situ from anhydride chlorides **66**.

A convenient two-step synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one 64b was developed using ionic liquids. The condensation of 4-methylthiazol-2-amine 1b with Meldrum's acid and trimethylorthoformate in a solution of 1-butyl-3-

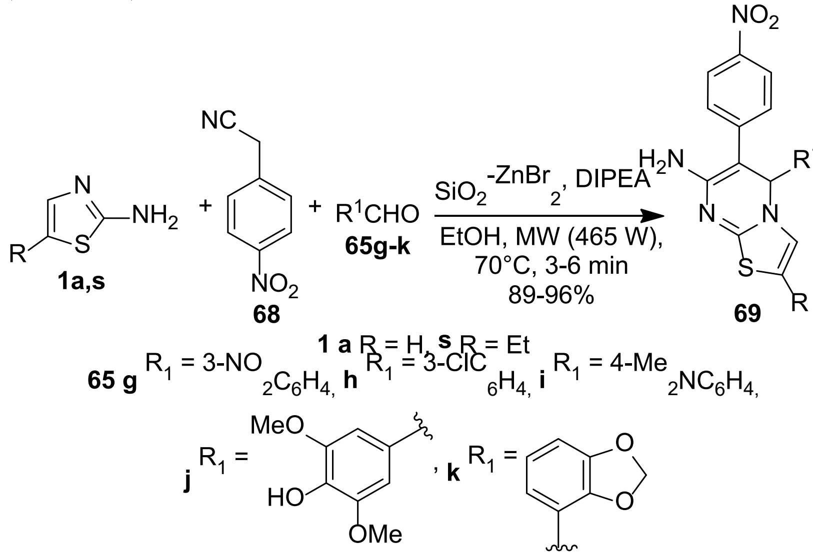
methylimidazolium bromide ([BMIM]Br) produced isopropylidene *N*-thiazolaminomethylenemalonate 27b, which upon cyclization in the 1-butyl-3-methyl tetrafluoroborate/triflate system was converted to the target product 19 (Scheme 25).[43]



Scheme 25. Two-step synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **64b** by condensation of 4-methylthiazol-2-amine **1b** with Meldrum's acid and trimethylorthoformate using an ionic liquid.

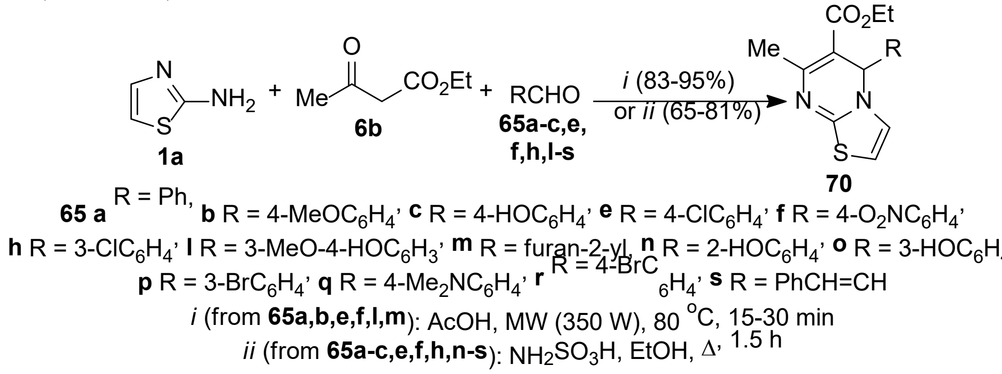
2.3. Multicomponent reactions based on 2-aminothiazoles

Three-component reactions are a convenient tool for the construction of thiazolo[3,2-*a*]pyrimidines due to the one-pot formation of C–C and C–N bonds. For instance, 2,5-substituted-6-(4-nitrophenyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-7-amines 69 were synthesized by the Biginelli type reaction of thiazol-2-amines 1a,s, 2-(4-nitrophenyl)acetonitrile 68 and aromatic aldehydes 65, promoted by a heterogeneous catalyst SiO_2–$ZnBr_2$ and diisopropylethylamine (DIPEA) as a base, under microwave irradiation (Scheme 26).[44]



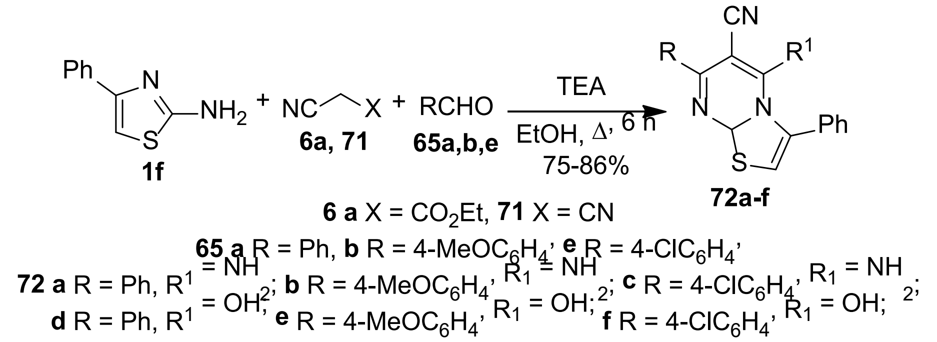
Scheme 26. Construction of thiazolo[3,2-*a*]pyrimidines **69** by the Biginelli type reaction of thiazol-2-amines **1**, 2-(4-nitrophenyl)acetonitrile **68** and aromatic aldehydes **65** promoted by SiO_2–$ZnBr_2$ and DIPEA.

The synthesis of 5-substituted 7-methyl-5*H*-thiazolo[3,2-*a]*pyrimidine-6-carboxylates **70** was realised by a one-pot reaction of 2-aminothiazole **1a**, ethyl acetoacetate **6b**, and aromatic aldehydes **65** under microwave irradiation in acetic acid solution (**Scheme 27**).[45] The authors[46] performed a similar reaction in boiling ethanol in the presence of catalytic amounts of sulfamic acid (**Scheme 27**).



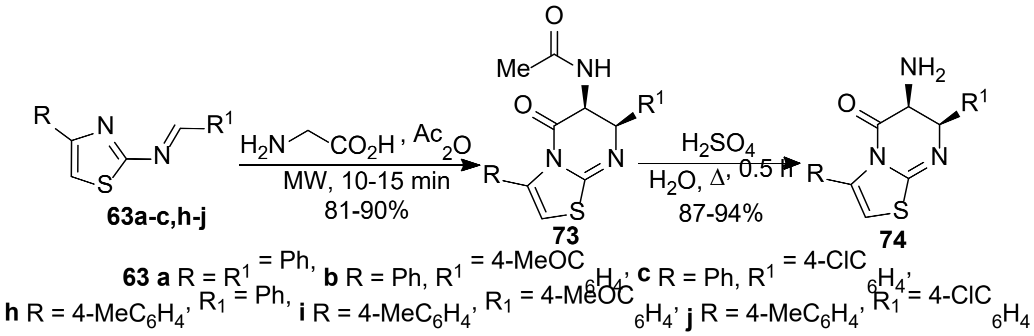
Scheme 27. Synthesis of 7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **70** by the one-pot reaction of 2-aminothiazole **1a**, ethyl acetoacetate **6b**, and aromatic aldehydes **65** under MW irradiation.

The one-pot three-component reaction of 4-phenylthiazol-2-amine **1f**, ethyl cyanoacetate **6a**, and malononitrile **71** with benzaldehydes **65** in ethanol in the presence of triethylamine produced 5,7-disubstituted 2-phenyl-8*aH*-thiazolo[3,2-*a*]pyrimidine-6-carbonitriles **72** in high yields (**Scheme 28**).[13]



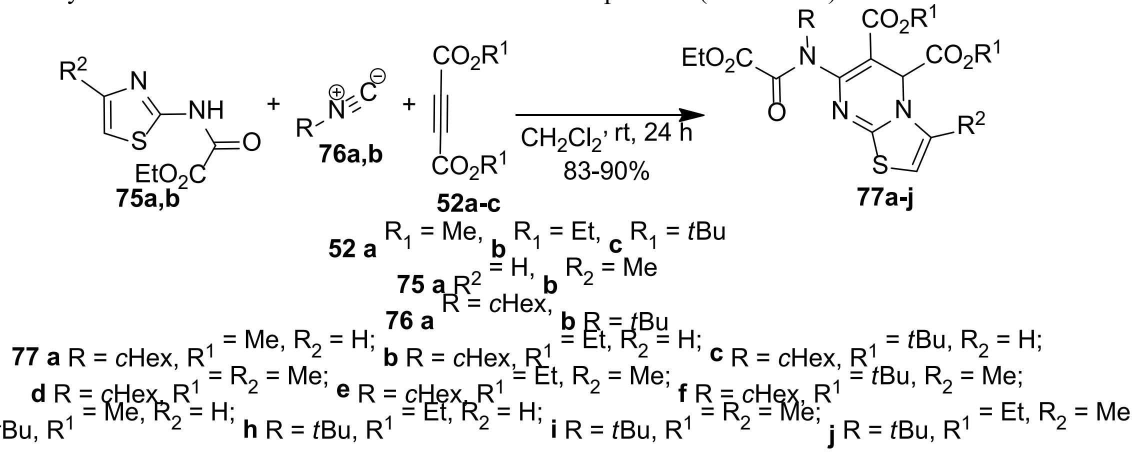
Scheme 28. Synthesis of 5,7-disubstituted 2-phenyl-8*aH*-thiazolo[3,2-*a*]pyrimidine-6-carbonitriles **72** by a one-pot three-component reaction of 4-phenylthiazol-2-amine **1f**, ethyl cyanoacetate **6a**, and malononitrile **71** with benzaldehydes **65**.

Diastereoselective annelation of the pyrimidine nucleus to form 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 73 was achieved by the interaction of Schiff bases 63, glycine, and acetic anhydride under microwave irradiation in the absence of solvent. The resulting *N*-acetylthiazolopyrimidinones 73 are readily hydrolyzed to the corresponding 6-amino derivatives 74 in high yields (Scheme 29).[47]



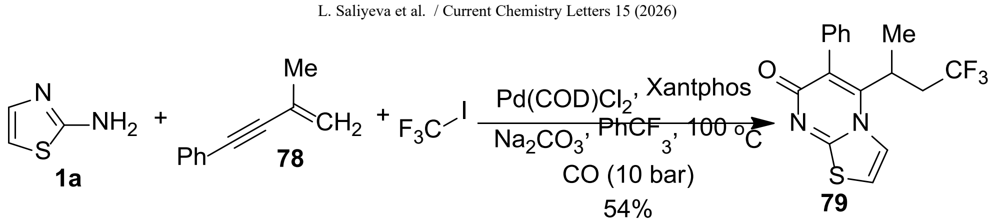
Scheme 29. Synthesis of 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **73** by the interaction of Schiff bases **63**, glycine, and acetic anhydride under MW irradiation.

The article[48] describes a novel synthesis of highly functionalized 5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines **77** by the three-component reaction of ethyl 2-oxo-2-(1,3-thiazol-2-ylamino)acetates **75**, isocyanides **76**, and dialkyl acetylenedicarboxylates **52** in dichloromethane solution at room temperature (**Scheme 30**).



Scheme 30. Synthesis of highly functionalized 5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines **77** by three-component reaction of ethyl 2-oxo-2-(1,3-thiazol-2-ylamino)acetates **75**, isocyanides **76** and dialkyl acetylenedicarboxylates **52**.

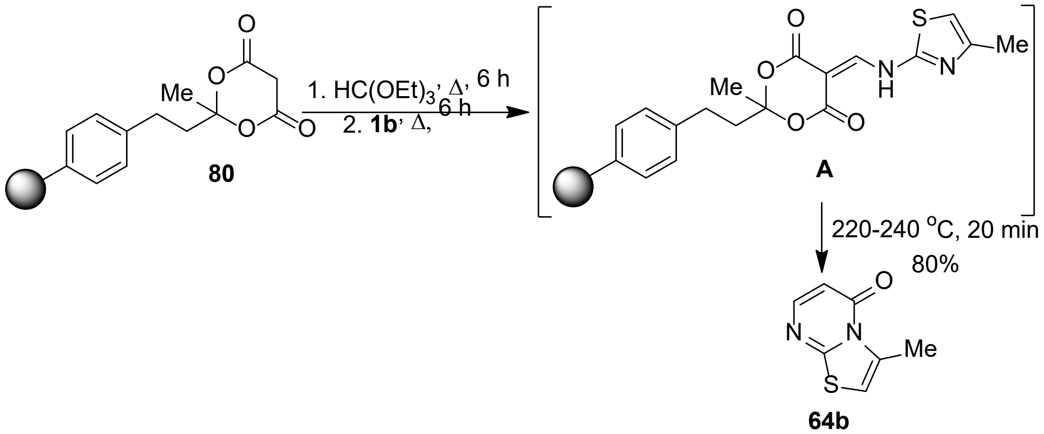
The authors[49] developed an efficient protocol for the Pd-catalyzed multicomponent fluoroalkylation carbonylation of 1,3-enyne **78** with 2-aminothiazole **1a**, and synthesized fluoroalkyl-substituted thiazolo[3,2-*a*]pyrimidin-7-one **79** (**Scheme 31**).



Scheme 31. Pd-catalyzed four-component synthesis of thiazolo[3,2-*a*]pyrimidine **79**.

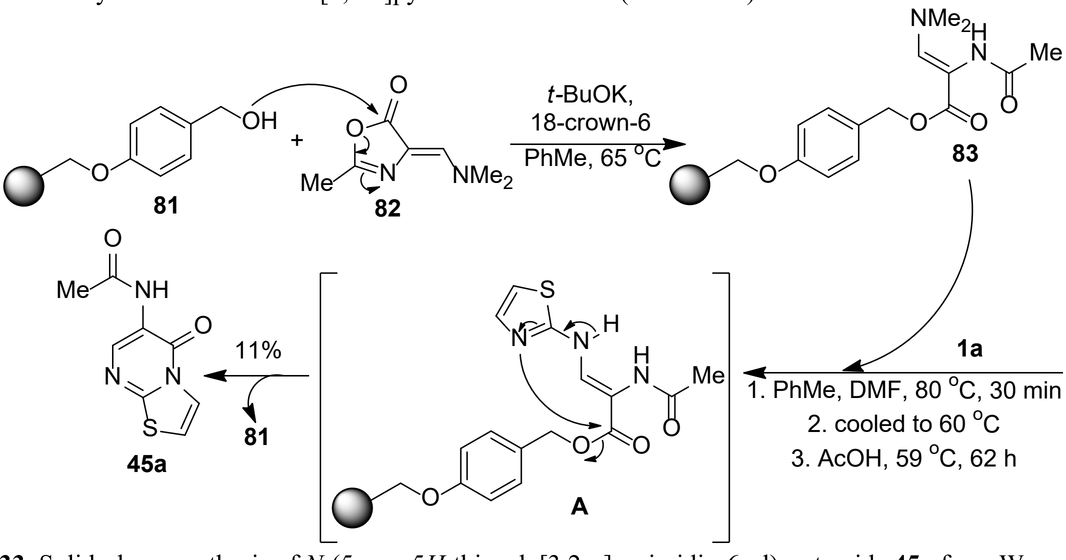
2.4. Solid-phase synthesis based on 2-aminothiazoles

The work[50] describes a solid-phase synthesis of 3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **64b** based on a polymer-bound analogue of Meldrum's acid **80**, the interaction of which with triethyl orthoformate and 4-methylthiazol-2-amine **1b** gave intermediate **A**, which upon thermolysis led to the target product **64b** in 80% yield (**Scheme 32**).



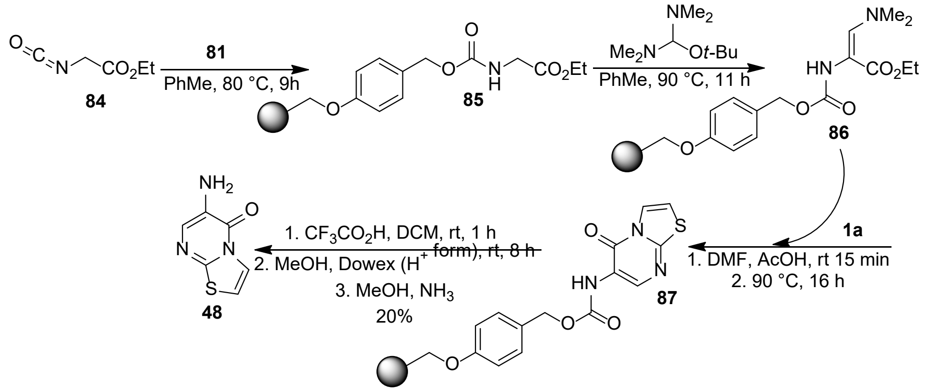
Scheme 32. Solid-phase synthesis of 3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **64b** by the reaction of Meldrum's acid analogue **80** with triethyl orthoformate and 4-methylthiazol-2-amine **1b**.

A solid-phase approach was used for the synthesis of *N*-(5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)acetamide 45a. Base-catalyzed treatment of Wang resin 81 with oxazolone 82 in toluene produced polymer-bound methyl 2-acetylamino-3-(dimethylamino)prop-2-enoate 83, which upon treatment with excess 2-aminothiazole 1a formed intermediate A and upon heating led to 6-acetylamino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one 45a (Scheme 33).[51]



Scheme 33. Solid-phase synthesis of *N*-(5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)acetamide **45a** from Wang resin **81**, oxazolone **82** and 2-aminothiazole **1a**.

6-Amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **48** was synthesized by a parallel solid-phase method from polymer-bound (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate **86**, which was obtained by treatment of Wang resin **81** with ethyl 2-isocyanatoacetate **84** followed by reaction with Bredereck's reagent. Further reaction of derivative **86** with 2-aminothiazole **1a** led to immobilized thiazolo[3,2-*a*]pyrimidine **87**, from which the target 6-aminothiazolopyrimidine **48** was obtained in 20% yield by standard technique (**Scheme 34**).[30]

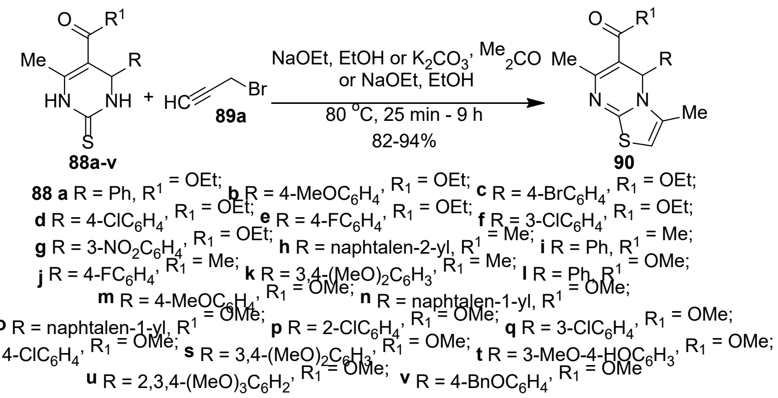


Scheme 34. Two-step solid-phase synthesis of 6-aminothiazolo[3,2-*a*]pyrimidine **48** by treatment of Wang resin **81** with ethyl 2-isocyanatoacetate **84**, followed by reaction with Bredereck's reagent and 2-aminothiazole **1a**.

3. Annelation of the thiazole nucleus to the pyrimidine ring

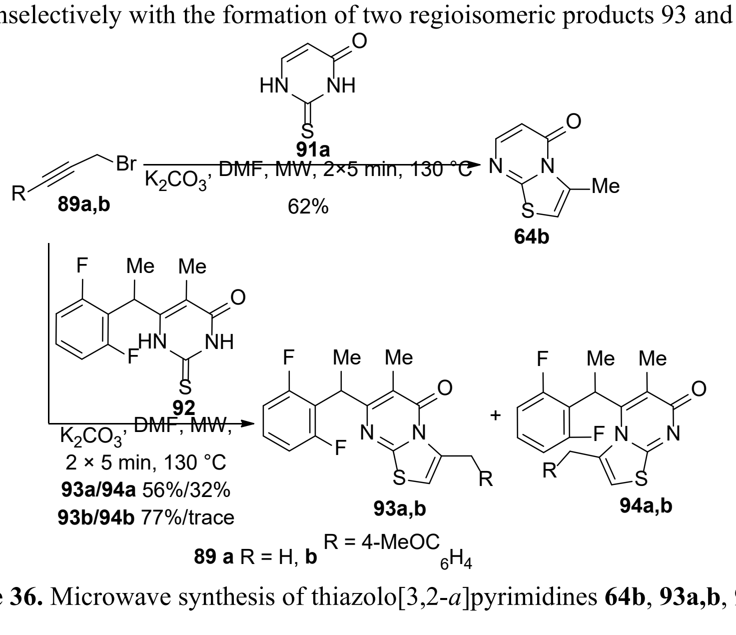
3.1. Cyclocondensation of pyrimidine-2-thiones with a monohalogen derivatives

A simple and efficient way to construct a thiazolo[3,2-*a*]pyrimidine core is the cyclocondensation of pyrimidine-2-thiones with functionalized alkyl halides. For instance, the reaction of 5-acyl-2-thioxo-1,2,3,4-tetrahydropyrimidines 88 with propargyl bromide 89a in boiling alcohol in the presence of a base produced a library of 6-acyl-5-aryl-5*H*-thiazolo[3,2-*a*]pyrimidines 90 (Scheme 35).[52]



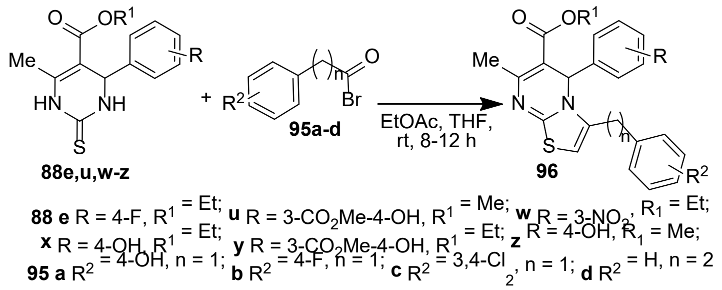
Scheme 35. Synthesis of 6-acyl-5-aryl-5*H*-thiazolo[3,2-*a*]pyrimidines **90** by the reaction of 2-thioxo-1,2,3,4-tetrahydropyrimidines **88** with propargyl bromide **89a**.

A microwave variant of this method was tested on the example of 2-thiouracil 91a which reacted with propargyl bromide 89a to yield 3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one 64b. However, a similar reaction of the 5,6-disubstituted derivative 91 proceeded nonselectively with the formation of two regioisomeric products 93 and 94 (Scheme 36).[53]



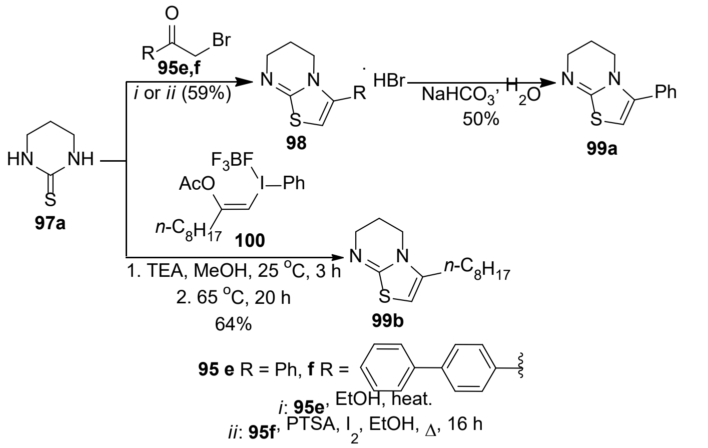
Scheme 36. Microwave synthesis of thiazolo[3,2-*a*]pyrimidines **64b**, **93a,b**, **94a,b**.

A convenient way of simultaneous construction and functionalization of the thiazolopyrimidine core is the cyclocondensation of 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **88** with acyl bromides **95** (**Scheme 37**).[54]



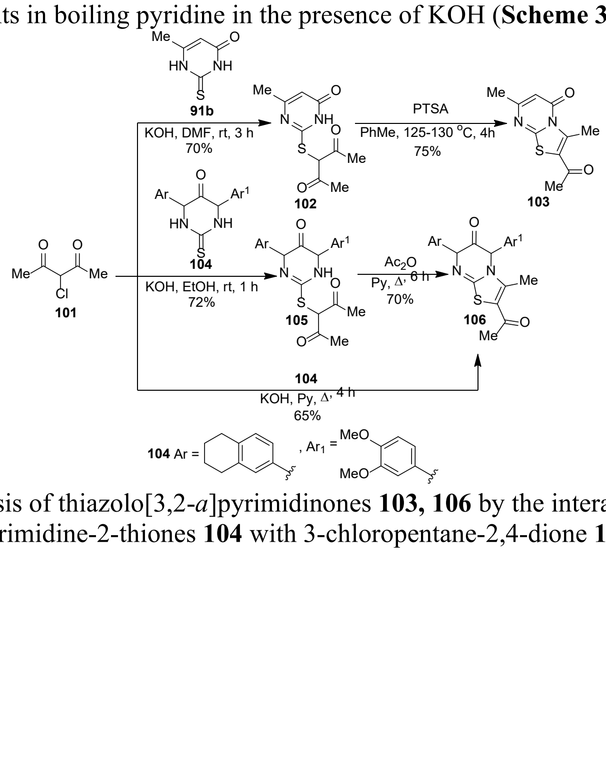
Scheme 37. Synthesis of thiazolo[3,2-*a*]pyrimidines **96** by cyclocondensation of 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **88** with acyl bromides **95**.

The synthesis of 3-substituted 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **97** was realised by cyclocondensation of tetrahydropyrimidine-2(1*H*)-thione **97a** with phenacyl bromides **95e,f** in boiling alcohol with subsequent neutralization with $NaHCO_3$ to the free base **99a**[55] or in boiling ethanol in the presence of the I_2/PTSA system[56]. To obtain 3-substituted 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine **99b**, the authors[57] used condensation with α-λ^3-iodanyl ketone **100** in the presence of triethylamine (TEA) (**Scheme 38**).



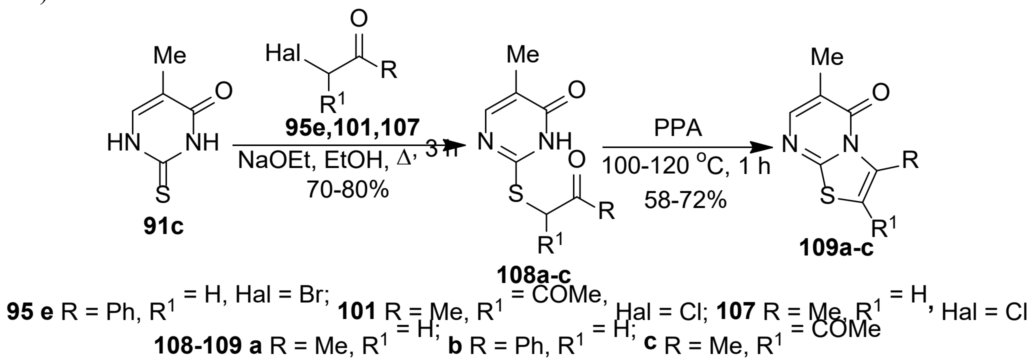
Scheme 38. Synthesis of 3-substituted 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **98, 99** by the reaction of tetrahydropyrimidine-2(1*H*)-thione **97a** with phenacyl bromides **95** or α-λ^3-iodanyl ketone **100**.

A simple method for the preparation of 2-acetyl-3,7-dimethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **103** involves the alkylation of 6-methylthiouracil **91b** with 3-chloropentane-2,4-dione **101** and subsequent regioselective cyclization of intermediate **102** with catalytic amounts of PTSA to the target product **103** (**Scheme 39**).[58] The synthesis of isomeric thiazolo[3,2-*a*]pyrimidin-6-one **106** was achieved by two routes, alkylation of pyrimidine-2-thione **104** with 3-chloropentane-2,4-dione **101** followed by intramolecular cyclization upon treatment with acetic anhydride, or by one-step cyclocondensation of the reactants in boiling pyridine in the presence of KOH (**Scheme 39**).[59]



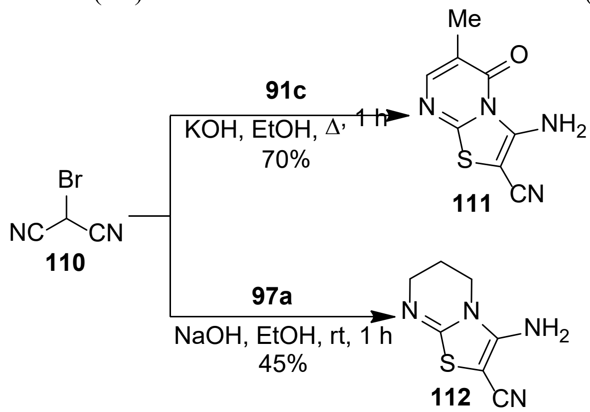
Scheme 39. Two-step synthesis of thiazolo[3,2-*a*]pyrimidinones **103, 106** by the interaction of 6-methylthiouracil or pyrimidine-2-thiones **104** with 3-chloropentane-2,4-dione **101**.

The reaction of 5-methylthiouracil **91c** with α-haloketones **95e, 101, 107** produced *S*-alkylated derivatives **108**, whose intramolecular cyclization under the action of polyphosphoric acid (PPA) leads to substituted thiazolo[3,2-*a*]pyrimidines **109** (**Scheme 40**).[60]



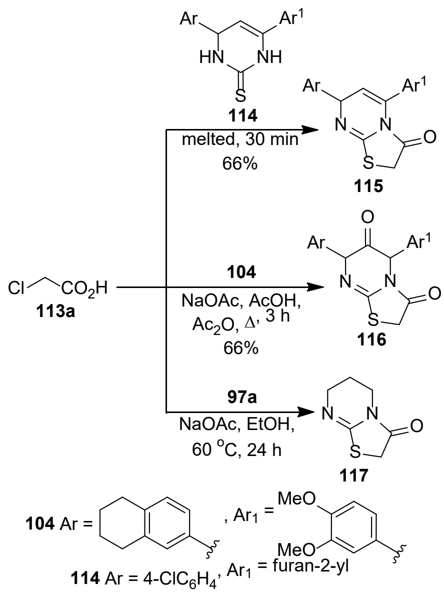
Scheme 40. Synthesis of thiazolo[3,2-*a*]pyrimidin-5-ones **109** by alkylation of 5-methylthiouracil **91c** with α-haloketones **95, 100, 107**.

A convenient option for the synthesis of 3-aminothiazolo[3,2-*a*]pyrimidine-2-carbonitriles **111, 112** is the reaction of thiouracil **91c**[60] or tetrahydropyrimidine-2(1*H*)-thione **97a**[61] with bromomalonitrile **110** (**Scheme 41**).



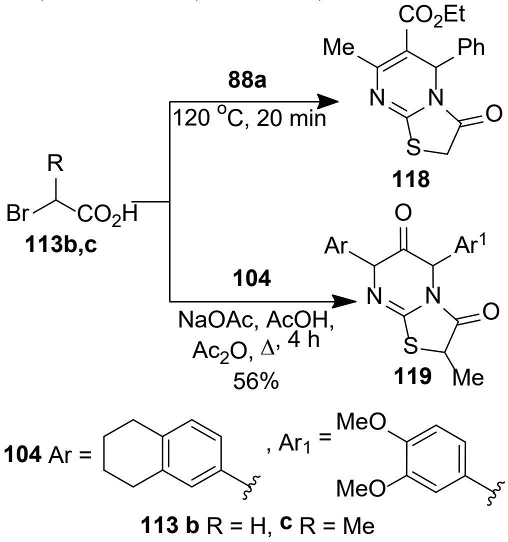
Scheme 41. Synthesis of 3-aminothiazolo[3,2-*a*]pyrimidine-2-carbonitriles **111, 112** by the reaction of pyrimidine-2-thiones **91c** or **97a** with bromomalonitrile **110**.

The most common method for preparing thiazolo[3,2-*a*]pyrimidin-3-ones is the cyclocondensation of pyrimidine-2-thiones with α-halocarboxylic acids. This transformation with chloroacetic acid **113a** was tested on 4,6-diaryl-3,4-dihydropyrimidine-2-thione **114**,[62] 4,6 diaryl-2-thioxotetrahydropyrimidin-5(2*H*)-one **104**[59] and tetrahydropyrimidine-2(1*H*)-thione **97a**[63] (**Scheme 42**).



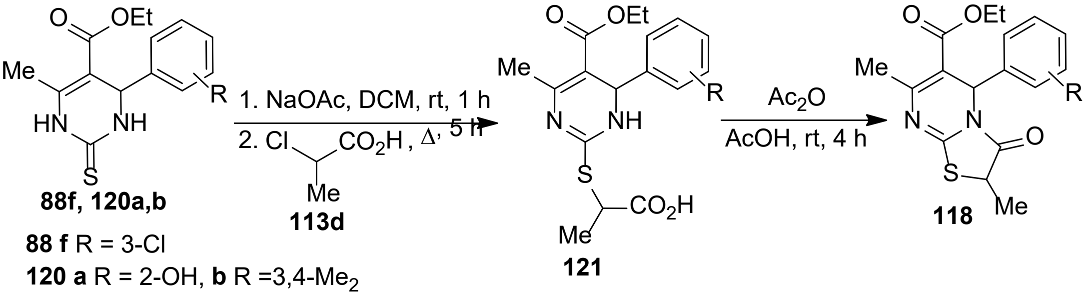
Scheme 42. Synthesis of thiazolo[3,2-*a*]pyrimidinones **115-117** by cyclocondensation of pyrimidine-2-thiones **97, 104, 114** with chloroacetic acid **113a**.

The interaction of bromoacetic acid **113b** with ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **88a** produced ethyl 7-methyl-3-oxo-5-phenyl-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **118**,[64] and 2-bromopropanoic acid **113c** with 4,6-diaryl-2-thioxotetrahydropyrimidin-5(2*H*)-one **104** yielded 5,7-diaryl-2-methyl-2*H*-thiazolo[3,2-*a*]pyrimidine-3,6(5*H*,7*H*)-dione **119**[59] (**Scheme 43**).



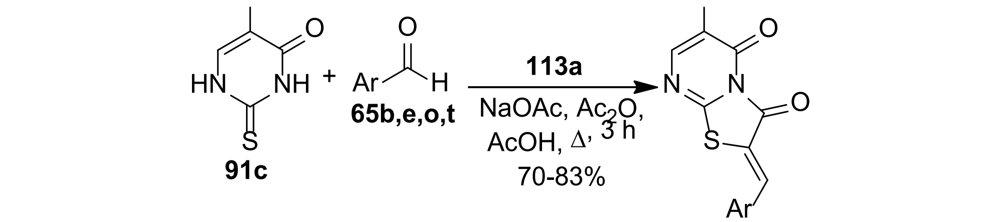
Scheme 43. Synthesis of thiazolo[3,2-*a*]pyrimidines **118, 119** by cyclocondensation of 2-bromocarboxylic acids **113** and pyrimidine-2-thiones **88, 104**.

The synthesis of ethyl 7-methyl-3-oxo-5-aryl-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **118** by alkylation of ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **88f, 120a,b** with 2-chloropropanoic acid **113d** and subsequent intramolecular cyclization of intermediates **121** in the presence of acetic anhydride was described in[65] (**Scheme 44**).



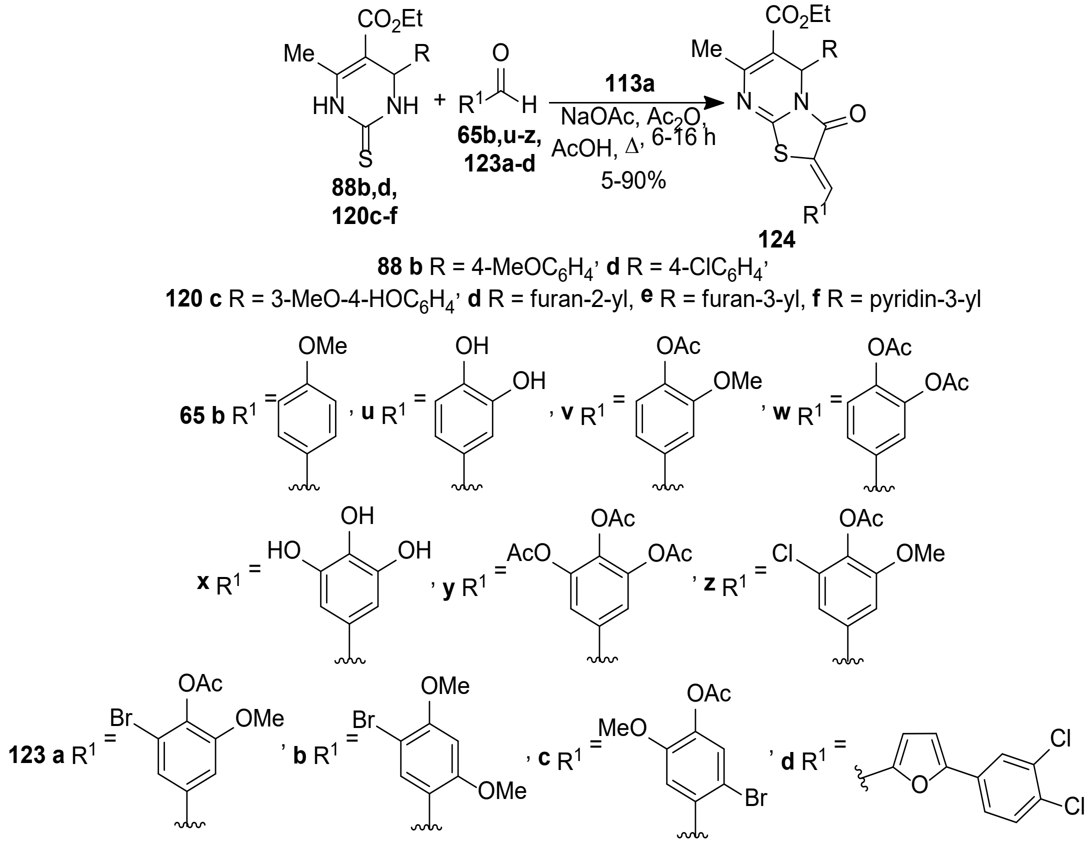
Scheme 44. Synthesis of ethyl 7-methyl-3-oxo-5-aryl-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **118** by alkylation of 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **88, 120** with 2-chloropropanoic acid **113d**.

The one-pot three-component reaction of 5-methylthiouracil **91c,** chloroacetic acid **113a**, and (hetero)aromatic aldehydes **65** is a convenient and efficient way to construct arylidene-functionalized thiazolo[3,2-*a*]pyrimidin-3-ones **122** (**Scheme 45**).[60]



Scheme 45. Synthesis of 2-arylidenethiazolo[3,2-*a*]pyrimidine-3,5-diones **122** by the reaction of 5-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **91c** with chloroacetic acid **113a** and aldehydes **65**.

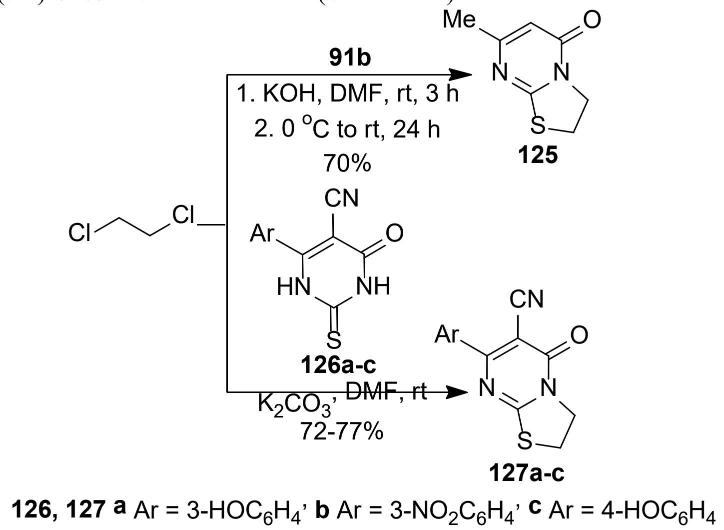
Similar reaction conditions were used to generate a combinatorial library of ethyl 2-arylidene-7-methyl-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **124**, potential inhibitors of protein kinase CK2 (**Scheme 46**).[66]



Scheme 46. Synthesis of ethyl 2-arylidene-7-methyl-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **124** by three-component reaction of pyrimidine-2-thiones **88, 120**, chloroacetic acid **113a** and (hetero)aromatic aldehydes **65, 123**.

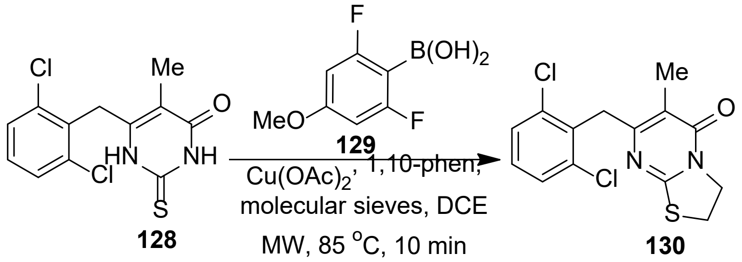
3.2. Cyclocondensation of pyrimidine-2-thiones with dihalogen derivatives

The cyclocondensation of pyrimidine-2-thiones with 1,2-dihaloalkanes is widely used for the synthesis of thiazolo[3,2-*a*]pyrimidine systems with a saturated thiazole core. For instance, the interaction of 6-methyl-2-thiouracil 91b with or 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyridine-5-carbonitriles 126 with 1,2-dichloroethane in a DMF solution produced thiazolo[3,2-*a*]pyrimidin-5(3*H*)-ones 125[58] and 127a-c[67] (**Scheme 47**).



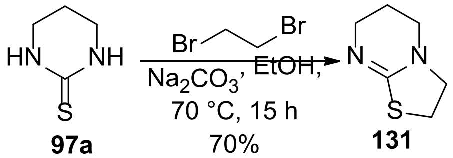
Scheme 47. Synthesis of 2,3-dihydrothiazolo[3,2-*a*]pyrimidines **125** and **127a-c** by cyclocondensation of pyrimidine-2-thiones **91** and **126 a-c** with 1,2-dichloroethane.

The result of the interaction of 5-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **128** with 2,6-difluoro-4-methoxyphenylboronic acid **129** under MW irradiation was unexpected, in which instead of the expected *S*-arylpyrimidinone, a cyclocondensation product with 1,2-dichloroethane **130** was obtained (**Scheme 48**).[68]



Scheme 48. Microwave option for the preparation of thiazolo[3,2-*a*]pyrimidin-5-one **130**.

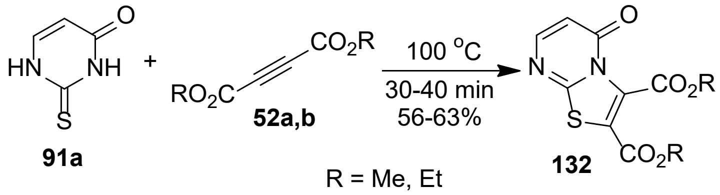
Cyclocondensation of tetrahydropyrimidine-2(1*H*)-thione **97a** with 1,2-dibromoethane in boiling alcohol in the presence of Na_2CO_3 yielded 2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine **131**, which, together with YCl_3 (ITU/YCl_3), was used for homo- and copolymerization processes (**Scheme 49**).[3]



Scheme 49. Synthesis of 2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine **131** by cyclocondensation of tetrahydropyrimidine-2(1*H*)-thione **97a** with 1,2-dibromoethane.

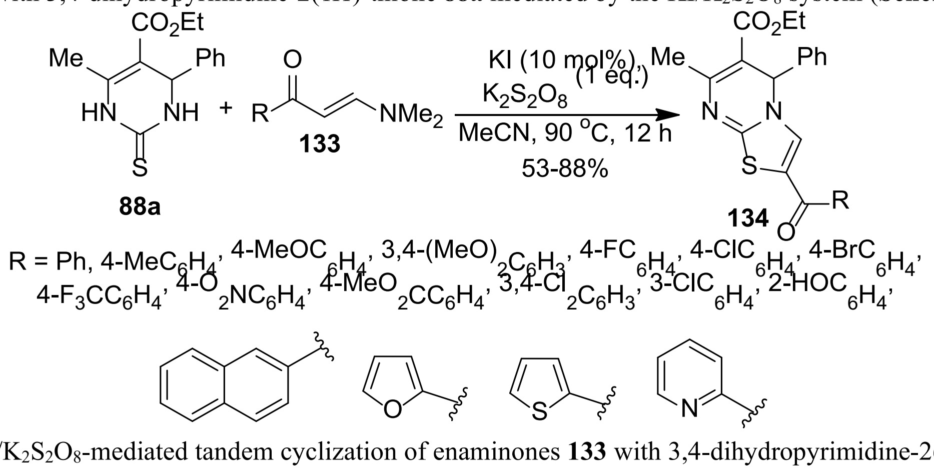
3.3. Other types of cyclocondensation involving pyrimidine-2-thiones

The thermal two-component reaction of 2-thiouracil **91a** and dialkyl acetylenedicarboxylates **52a,b** leads to the formation of dialkyl 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3-dicarboxylates **132** under mild conditions (**Scheme 50**).[69]



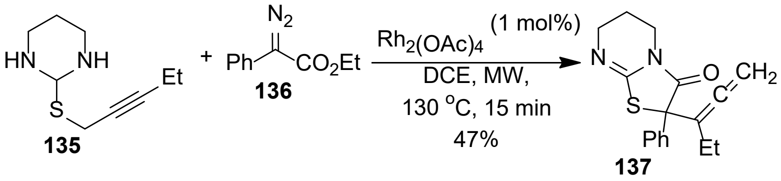
Scheme 50. Synthesis of dialkyl 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3-dicarboxylates **132** by cyclocondensation of 2-thiouracil **91a** and dialkyl acetylenedicarboxylates **52**.

A new strategy for the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidines **134** was based on the tandem cyclization of enaminones **133** with 3,4-dihydropyrimidine-2(1*H*)-thione **88a** mediated by the KI/$K_2S_2O_8$ system (**Scheme 51**).[70]



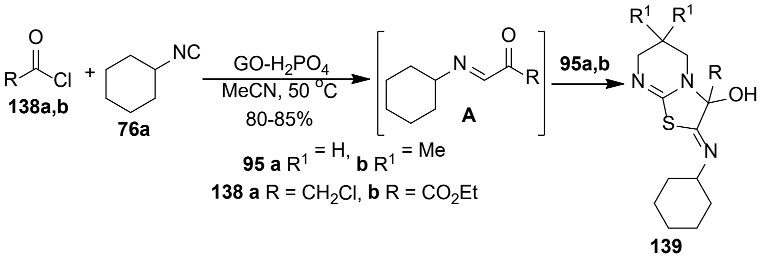
Scheme 51. KI/$K_2S_2O_8$-mediated tandem cyclization of enaminones **133** with 3,4-dihydropyrimidine-2(1*H*)-thione **88a** for the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidines **134**.

The authors[71] used a rhodium-catalyzed domino reaction of 2-sulfenyltetrahydropyrimidine **135** with diazoester **136** to synthesize thiazolo[3,2-*a*]pyrimidine **137** (**Scheme 52**).



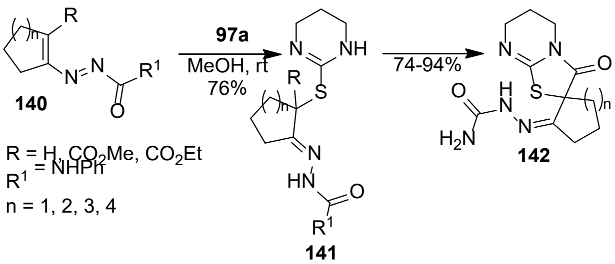
Scheme 52. Rh-catalyzed synthesis of thiazolo[3,2-*a*]pyrimidine **137**.

The work[72] describes a practical and efficient method for the synthesis of thiazolo[3,2-*a*]pyrimidines **139** by the three-component reaction of anhydride chlorides **138a,b**, isocyanide **76a**, and tetrahydropyrimidine-2(1*H*)-thiones **95** in the presence of phosphoric acid supported on graphene oxide (GO-H_2PO_4) (**Scheme 53**).



Scheme 53. Three-component synthesis of thiazolo[3,2-*a*]pyrimidines **139** catalyzed by the GO-H_2PO_4 system.

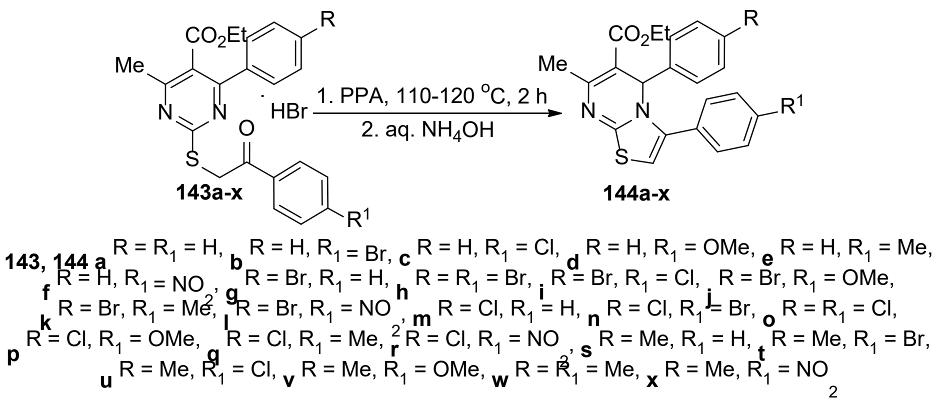
A one-pot two-step method for the synthesis of thiazolo[3,2-*a*]pyrimidines **142**, spiro-annelated with cycloalkane fragments, was implemented by the interaction of tetrahydropyrimidine-2-thione **97a** with cycloalkenyl-1-diazenes **140** in methanol at room temperature (**Scheme 54**).[73]



Scheme 54. Synthesis of spiro[cycloalkyl-1,2'-[1,3]thiazolo[3,2-*a*]pyrimidines] **142**.

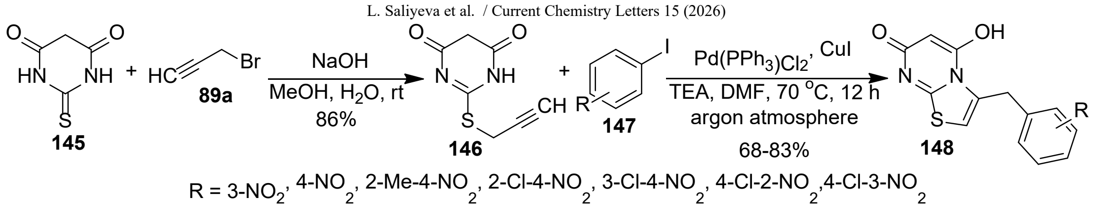
4. Other methods for the synthesis of thiazolo[3,2-*a*]pyrimidines

The authors[64] used proton-initiated cyclization of 2-phenacylthiopyrimidine hydrobromides **143** involving PPA for the synthesis of 3,5-diaryl-7-methylthiazolo[3,2-*a*]pyrimidine-6-carboxylates **144**, potential antimicrobial, antiexudative and analgesic agents (**Scheme 55**).



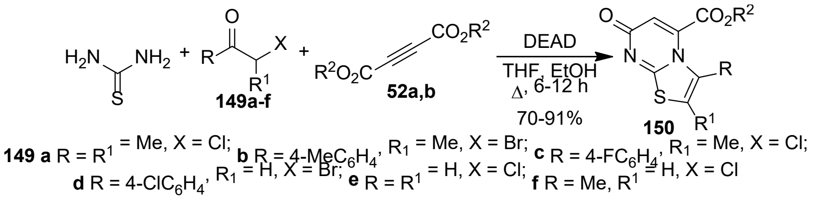
Scheme 55. Synthesis of 3,5-diaryl-7-methylthiazolo[3,2-*a*]pyrimidine-6-carboxylates **144a-x** by intramolecular cyclization of 2-phenacylthiopyrimidine hydrobromides **143a-x**.

An efficient method for the synthesis of 3-benzyl-[1,3]thiazolo[3,2-*a*]pyrimidinones **148** was realised by alkylation of thiobarbituric acid **145** with propargyl bromide **89** followed by cyclization of intermediate **146** under the action of aryl iodides **147** in the presence of a Pd-Cu catalyst complex (**Scheme 56**).[74]



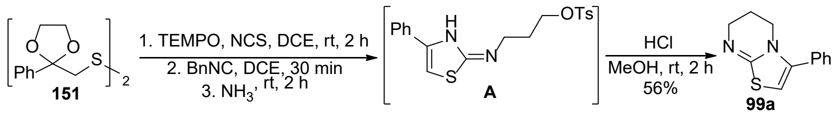
Scheme 56. Synthesis of 3-benzylthiazolo[3,2-*a*]pyrimidinones **148** via Pd/Cu-catalyzed coupling reaction of 6-hydroxy-2-(prop-2-yn-1-ylsulfanyl)pyrimidin-4(1*H*)-one **146** with aryl iodides **147**.

A one-pot three-component synthesis of thiazolo[3,2-*a*]pyrimidine-5-carboxylates **150** by the interaction of thiourea, α-haloketones **149a-f**, and dialkyl acetylenedicarboxylates **52a,b** in a THF-EtOH solvent mixture in the presence of diethyl azodicarboxylate (DEAD) was described in[75] (**Scheme 57**).



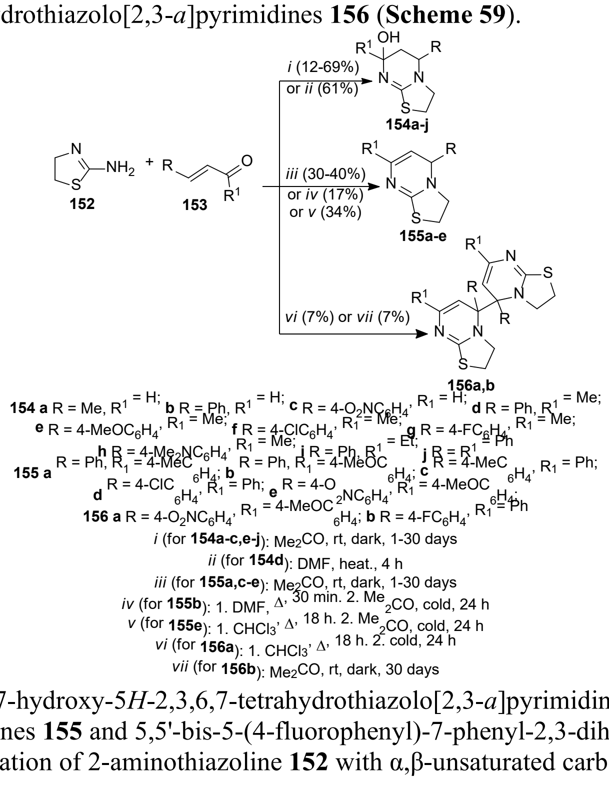
Scheme 57. Three-component synthesis of thiazolo[3,2-*a*]pyrimidine-5-carboxylates **150** by the reaction of thiourea, α-haloketones **149a-f** and dialkyl acetylenedicarboxylates **52a,b**.

A new one-pot multicomponent synthesis method was developed to obtain 3-phenyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine **99a**. It is based on the reaction of disulfide **151** with *N*-halosuccinimide in the presence of TEMPO followed by the action of isocyanide and a nucleophilic reagent, leading to intermediate **A**. Its treatment with a methanol solution of hydrogen chloride gives the target product **99a** (**Scheme 58**).[76]



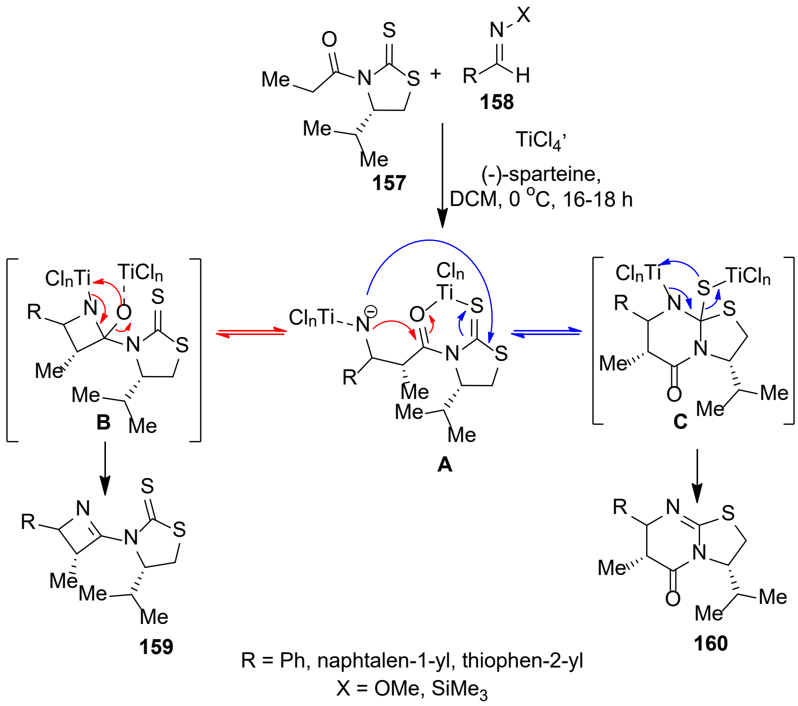
Scheme 58. Synthesis of 3-phenyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine **99a** from disulfide **151**.

The authors of the work[77] described the cyclocondensation reaction of 2-aminothiazoline **152** with α,β-unsaturated carbonyl compounds **153**, which under mild conditions enabled the synthesis of 7-hydroxy-5*H*-2,3,6,7-tetrahydrothiazolo[2,3-*a*]pyrimidines **154**, 5,7-diaryl-5*H*-2,3-dihydrothiazolo[2,3-*a*]pyrimidines **155** and 5,5'-bis-5-(4-fluorophenyl)-7-phenyl-2,3-dihydrothiazolo[2,3-*a*]pyrimidines **156** (**Scheme 59**).



Scheme 59. Synthesis of 7-hydroxy-5*H*-2,3,6,7-tetrahydrothiazolo[2,3-*a*]pyrimidines **154**, 5,7-diaryl-5*H*-2,3-dihydrothiazolo[2,3-*a*]pyrimidines **155** and 5,5'-bis-5-(4-fluorophenyl)-7-phenyl-2,3-dihydrothiazolo[2,3-*a*]pyrimidines **156** by cyclocondensation of 2-aminothiazoline **152** with α,β-unsaturated carbonyl compounds **153**.

7-Substituted (3*S*,6*R*)-3-isopropyl-6-methyl-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-ones **160** were unexpectedly obtained as by-products in the synthesis of *N*-azethynylthiozolidine-thiones **159** in ratios of 8:1 (R = Ph), 6:1 (R = naphthalen-1-yl) and 15:1 (R = thiophen-2-yl) (**Scheme 60**).[78,79]



Scheme 60. Synthesis of (3*S*,6*R*)-3-isopropyl-6-methyl-7-phenyl-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one **160** by the reaction of (*S*)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)propan-1-one **157** and oxime **158**.

5. Biomedical potential of thiazolo[3,2-*a*]pyrimidines

Functionalized thiazolo[2,3-*a*]pyrimidines are attractive targets for biomedical research. For instance, a number of compounds among the derivatives of this class are characterized by promising antibacterial and antifungal activities. Antibacterial screening of compounds of type 69 identified derivatives that are characterized by activity against the gram-negative bacteria *Pseudomonas aeruginosa* at the level of the medical drug tetracycline (MIC = 6.25 μg/ml).[44] Ethyl 7-methyl-5-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **70** is characterized by antibacterial activity against gram-positive bacteria *Micrococcus luteus*, *Bacillus subtilis* and gram-negative bacteria *Salmonella typhimurium*, *Bordetella bronchiseptica*, *Escherichia coli*.[46] Thiazolopyrimidine derivatives containing 3-nitrophenyl **127b** or 4-hydroxyphenyl **127c** groups exhibit a broad spectrum of antibacterial activity against gram-positive bacteria *Bacillus subtilis*, *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*.[67] Ethyl 7-methyl-5-phenyl-3-(*p*-tolyl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **144e** inhibits the growth of the gram-positive bacteria *Bacillus cereus*.[64] The modified thiazolo[2,3-*a*]pyrimidine **161**[21] demonstrated high activity against the gram-positive bacteria *Staphylococcus aureus* (**Fig. 2**).

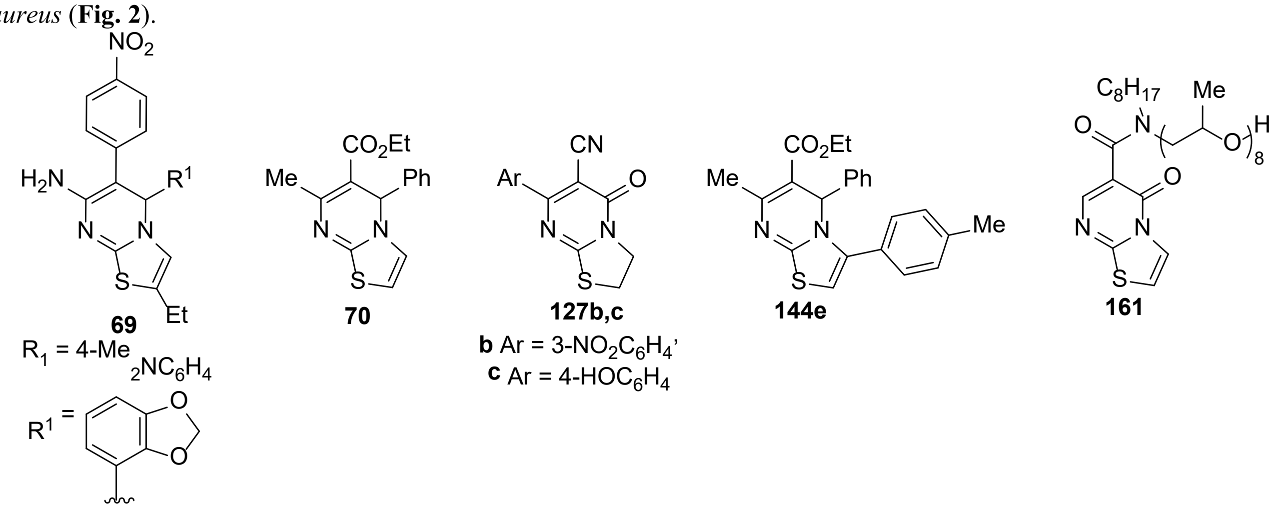
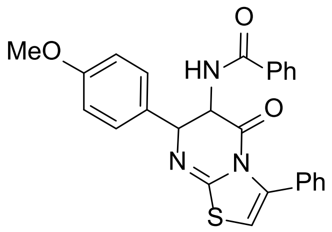


Fig. 2. Functionalized thiazolo[2,3-*a*]pyrimidines with antimicrobial activity.

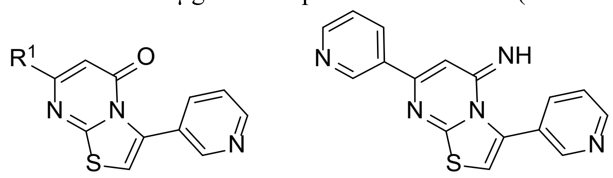
N-[7-(4-Methoxyphenyl)-5-oxo-3-phenyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]benzamide **50b** was tested for antifungal activity against *Aspergillus niger* and *Fusarium oxysporum* using the food poisoning method and demonstrated excellent fungicidal activity compared to the commercial fungicide Ditan M-45 (**Fig. 3**).[32]



50b

Fig. 3. *N*-[7-(4-Methoxyphenyl)-5-oxo-3-phenyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]benzamide **50b** with fungicidal activity.

3,7-Disubstituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 54 and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-imines 56 were evaluated as potential synthetic antioxidants for DPPH free radical inhibition. Derivatives 54a,b and 56a were found to scavenge 76.43-77.15% of radicals at a concentration of 100 μg/mL compared to the control (ascorbic acid *I* = 82%) (Fig. 4).[35]

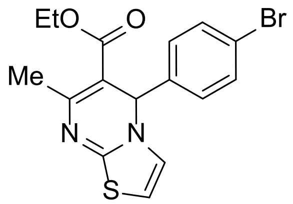


54a,b **56a**

54 a R_1 = Me, **b** R_1 = pyridin-3-yl

Fig. 4. Disubstituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **54** and 5*H*-thiazolo[3,2-*a]*pyrimidin-5-imines **56** with antioxidant activity against DPPH radicals.

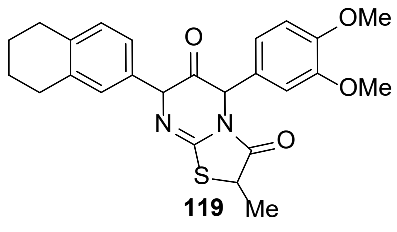
A derivative with antidiabetic potential was identified among the compounds of type **70**, which reduces the concentration of glucose in the blood plasma of mice to 25 mg/DL, while the medical drug glibenclamide used as a standard demonstrates a decrease to 98 mg/DL (**Fig. 5**).[46]



70

Fig. 5. Ethyl 5-(4-bromophenyl)-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **70** with antidiabetic activity.

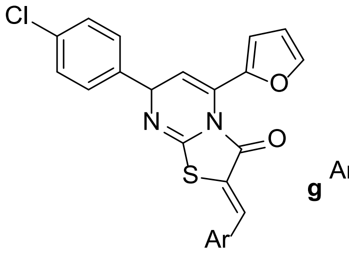
5-(3,4-Dimethoxyphenyl)-2-methyl-7-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-thiazolo[3,2-*a*]pyrimidine-3,6(5*H*,7*H*)-dione **119** is characterized by excellent antiviral activity and inhibits the herpes virus HSV-1 by 90% at a concentration of 2 μg/mL and by 100% at 5 μg/mL (**Fig. 6**).[59]



119

Fig. 6. 5-(3,4-Dimethoxyphenyl)-2-methyl-7-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-thiazolo[3,2-*a*]pyrimidine-3,6(5*H*,7*H*)-dione **119** is a potential antiviral agent.

2-Arylidenethiazolo[3,2-*a*]pyrimidin-3-ones 162 were evaluated for antinociceptive activity by the tail-flick method, anti-inflammatory activity by the carrageenan-induced paw edema test, and ulcerogenicity index. The bioscreening demonstrated that derivatives with substituents at the 4-position of the benzene ring (Me, OH, F, Cl, Br, NO_2) exhibited significant antinociceptive and anti-inflammatory activity. In particular, 2-(4-fluorobenzylidene)-7-(4-chlorophenyl)-5-(furan-2-yl)-2*H*-thiazolo[3,2-*a*]pyrimidin-3(7*H*)-one 162g was characterized by a broad spectrum of anti-inflammatory and antinociceptive activity with lower ulcerogenicity (Fig. 7).[62]

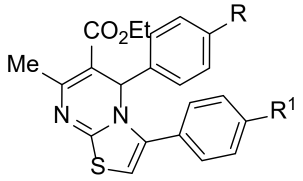


162a-j

162 a Ar = Ph, **b** Ar = 2-MeC$_6$H$_4$, **c** Ar = 2-HOC$_6$H$_4$, **d** Ar = 2-NO$_2$C$_6$H$_4$, **e** Ar = 4-MeC$_6$H$_4$, **f** Ar = 4-HOC$_6$H$_4$, **g** Ar = 4-FC$_6$H$_4$, **h** Ar = 4-ClC$_6$H$_4$, **i** Ar = 4-BrC$_6$H$_4$, **j** Ar = 4-NO$_2$C$_6$H$_4$

Fig. 7. 2-Arylidenethiazolo[3,2-*a*]pyrimidin-3-ones **162a-j** with antinociceptive and anti-inflammatory activities.

A library of 3,5-diaryl-7-methylthiazolo[3,2-*a*]pyrimidine-6-carboxylates 144 was tested for antiexudative activity. It was found that derivatives 144c,v demonstrate a gradual increase in their anti-inflammatory activity, reaching a maximum after 5 h. When testing the analgesic activity of compounds 144e,v, the maximum activity was also found after 5 h of injection (Fig. 8).[64]

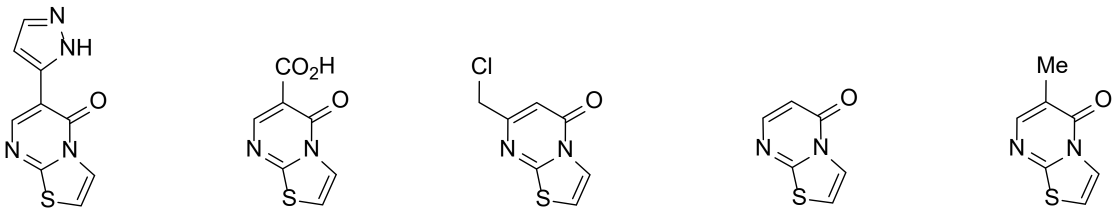


144c,e, v

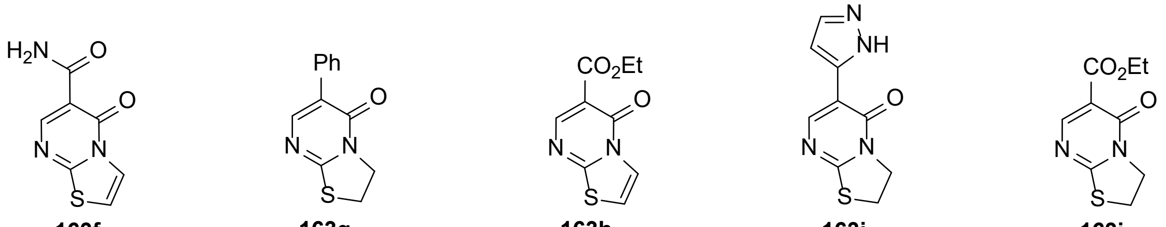
c R = H, R$_1$ = Cl,
e R = H, R$_1$ = Me,
v R = Me, R$_1$ = OMe

Fig. 8. Derivatives of 3,5-diaryl-7-methylthiazolo[3,2-*a*]pyrimidine-6-carboxylates **144**, characterized by antiexudative and analgesic activities.

A series of thiazolo[3,2-*a*]pyrimidine derivatives **163a-j** were identified in[80] as potential allosteric inhibitors of langerin, which makes them attractive for the development of chemical probes for mammalian C-type lectin receptors (CLRs) (**Fig. 9**).



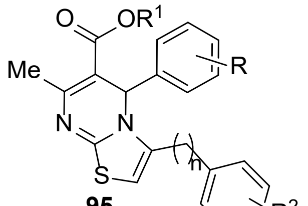
163a	**163b**	**163c**	**163d**	**163e**
$K_{D,app}$ = 0.7 ± 0.1 mM	$K_{D,app}$ = 0.7 ± 0.1 mM	$K_{D,app}$ = 1.7 ± 0.1 mM	$K_{D,app}$ = 9.1 ± 3.7 mM	$K_{D,app}$ = 3.2 ± 0.4 mM
LE = 0.28	LE = 0.33	LE = 0.31	LE = 0.28	LE = 0.31
IC_{50} = 0.6 ± 0.2 mM	IC_{50} = 0.3 ± 0.1 mM	IC_{50} = 0.4 ± 0.1 mM	IC_{50} = n.d. (>10 mM)	IC_{50} = n.d. (>10 mM)



163f	**163g**	**163h**	**163i**	**163j**
$K_{D,app}$ = 3.6 ± 0.3 mM	$K_{D,app}$ = 1.0 ± 0.1 mM	$K_{D,app}$ = 2.7 ± 0.2 mM	$K_{D,app}$ = 1.7 ± 0.1 mM	$K_{D,app}$ = 3.1 ± 0.1 mM
LE = 0.26	LE = 0.26	LE = 0.23	LE = 0.25	LE = 0.23
IC_{50} = 0.7 ± 0.2 mM	IC_{50} = n.d. (>4 mM)	IC_{50} = n.d. (>4 mM)	IC_{50} = n.d. (>10 mM)	IC_{50} = n.d. (>10 mM)

Fig. 9. Thiazolo[3,2-*a*]pyrimidine derivatives **163a-j**, mammalian lectin inhibitors.

A molecular docking study of the binding affinity of functionalized thiazolo[3,2-*a*]pyrimidine-6-carboxylates **95** with cyclophilin D (CypD) revealed 10 derivatives with the best inhibitory activity that could be used for the treatment of Alzheimer's disease (**Fig. 10**).[54]

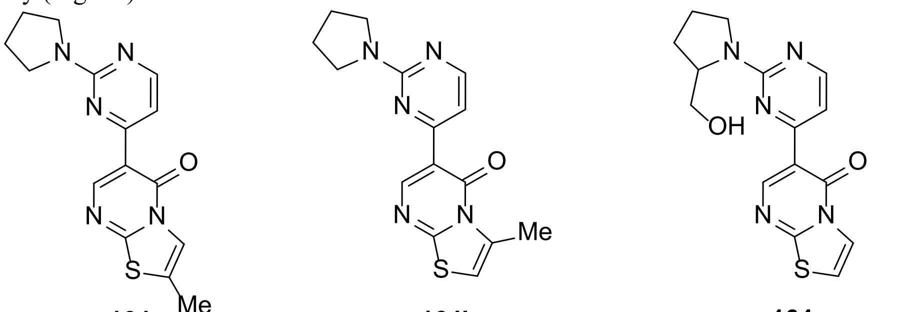


95

95 e R = 4-OH, R_1 = Et, R_2 = 4-F, n = 1; **f** R = 4-OH, R_1 = Et, R_2 = 3,4-Cl_2, n = 1;
h R = 4-F, R_1 = Et, R_2 = 4-F, n = 1; **i** R = 4-F, R_1 = Et, R_2 = 3,4-Cl_2, n = 1;
k R = 3-CO_2Me-4-OH, R^1 = Et, R_2 = 4-F, n = 1;
l R = 4-OH, R_1 = Me, R_2 = 4-OH, n = 1;
n R = 3-NO_2, R_1 = Et, n = 2; **o** R = 4-OH, R_1 = Et, n = 2; **p** R = 4-F, R_1 = Et, n = 2;

Fig. 10. Thiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives **95**, inhibitors of cyclophilin D (CypD).

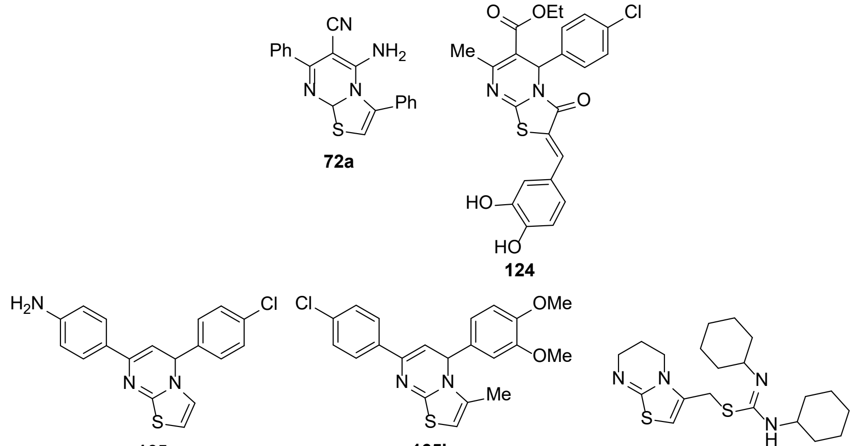
Derivatives with promising inhibitory activity against acetylcholinesterase (AChEI), a major target in the treatment of Alzheimer's disease, were identified in a series of 6-{2-(pyrrolidin-1-yl)pyrimidin-4-yl}thiazolo[3,2-*a*]pyrimidin-5-ones 164. In addition, compound 164c exhibits inhibitory activity similar to that of the FDA-approved drug galantamine, but with better selectivity (Fig. 11).[36]



164a IC_{50} = 13.10±0,53 µM **164b** IC_{50} = 16.02±0.46 µM **164c** IC_{50} = 6.22±0.54 µM

Fig. 11. 6-{2-(Pyrrolidin-1-yl)pyrimidin-4-yl}thiazolo[3,2-*a*]pyrimidin-5-ones **164**, acetylcholinesterase inhibitors (AChEI).

5-Amino-3,7-diphenyl-8*aH*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **72a** demonstrated higher efficinecy than the reference doxorubicin in *in vitro* screening against human cancer cell lines such as MCF-7 breast adenocarcinoma, NCI-H460 non-small cell lung cancer, and SF-268 CNS cancer.[13] In turn, 5-(4-chlorophenyl)-2-(3,4-dihydroxybenzylidene)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **124** inhibited the independent protein kinase CK2 (IC_{50} = 0.56 µM) 2.2-fold more effectively than 4,5,6,7-tetrabromobenzotriazole (TBB IC_{50} = 1.24 µM). Treatment of cells with compound **124** inhibited endogenous PKCK2 activity and exhibited antiproliferative and proapoptotic effects against gastric cancer cell lines and hepatocytes more effectively than TBB.[66] Among the library of 5,7-diaryl-substituted thiazolo[3,2-*a*]pyrimidines **165** that were evaluated *in vitro* for anticancer activity, compounds **165a,b** were found with sensitivity to non-small cell lung cancer Hop-92, ovarian cancer IGROV1, and melanoma SK-MEL-2.[10] The carbamidothioate-modified 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine **166**[81] is a selective inhibitor of the chemokine receptor CXCR4, which is involved in hematopoiesis, immune cell migration, cancer metastasis, and functions as a coreceptor for the viral envelope protein gp120 (**Fig. 12**).



72a **124**

165a GI_{50} = 5.0%, TGI = 19.5% LC_{50} = 52.5%

165b GI_{50} = 5.89%, TGI = 20.0% LC_{50} = 66.1%

166 IC_{50} (bind.) = 185 nM IC_{50} (Ca^{2+}) = 57 nM

Fig. 12. Some examples of thiazolo[3,2-*a*]pyrimidines with anticancer activity.

6. Conclusions

A detailed analysis of the literature has shown that in most cases the construction of a thiazolo[3,2-*a*]pyrimidine system involves the annelation of the pyrimidine nucleus to the thiazole ring or the addition of the thiazole nucleus to the pyrimidine ring. However, in recent years, metal-catalyzed reactions, rearrangements, and one-pot methods for constructing the thiazolopyrimidine nucleus have become more attractive. The promising complex of biological properties makes them very promising structures for controlled modification with the aim of developing pharmacologically active substances.

References

1 Leysen J. E., Van Gompel P., Gommeren W., Woestenborghs R., Janssen P. A. J. (**1986**) Down Regulation of Serotonin-S2 Receptor Sites in Rat Brain by Chronic Treatment with the Serotonin-S2 Antagonists: Ritanserin and Setoperone. *Psychopharmacology*, 88 (4) 434–444.

2 Birman V. B., Li X. (**2008**) Homobenzotetramisole: An Effective Catalyst for Kinetic Resolution of Aryl-Cycloalkanols. *Org. Lett.*, 10 (6) 1115–1118.

3 Wang Y., Han Y., Zhang L. (**2020**) Binary Catalytic System for Homo- and Block Copolymerization of ε-Caprolactone with δ-Valerolactone. *RSC Adv.*, 10 (43) 25979–25987.

4 Chaban Z., Harkov S., Chaban T., Klenina O., Ogurtsov V., Chaban I. (**2017**) Recent Advances in Synthesis and Biological Activity Evaluation of Condensed Thiazoloquinazolines: A Review. *Pharmacia*, 64 (3) 52–66.

5 Khandelwal S., Tailor Y. K., Rushell E., Kumar M. (**2020**) Use of Sustainable Organic Transformations in the Construction of Heterocyclic Scaffolds. In Green Approaches in Medicinal Chemistry for Sustainable Drug Design, Elsevier, 245–352.

6 Sączewski J., Fedorowicz J. (**2022**) Three Heterocyclic Rings Fused (6-5-6). In Comprehensive Heterocyclic Chemistry IV, Elsevier, 569–596.

7 Slivka M. V., Fizer M. M., Korol N. I. (**2022**) Three Heterocyclic Rings Fused (5-6-6). In Comprehensive Heterocyclic Chemistry IV, Elsevier, 527–568.

8 Prakash C., Singh R. (**2024**) Synthesis of Fluorinated Six-Membered Nitrogen Heterocycles Using Microwave Irradiation. *Chem. Heterocyclic Comp.*, 60 (5–6) 216–229.

9 Islam Md. R., Fahmy H. (**2022**) Thiazolopyrimidine Scaffold as a Promising Nucleus for Developing AnticancerDrugs: A Review Conducted in Last Decade. *Anti-cancer Agents Med. Chem.*, 22 (17) 2942–2955.

10 Hassan G. S., El-Messery S. M., Abbas A. (**2017**) Synthesis and Anticancer Activity of New Thiazolo[3,2-*a*]pyrimidines: DNA Binding and Molecular Modeling Study. *Bioorg. Chem.*, 74 41–52.

11 Al-Rashood S. T., Elshahawy S. S., El-Qaias A. M., El-Behedy D. S., Hassanin A. A., El-Sayed S. M., El-Messery S. M., Shaldam M. A., Hassan G. S. (**2020**) New Thiazolopyrimidine as Anticancer Agents: Synthesis, Biological Evaluation, DNA Binding, Molecular Modeling and ADMET Study. *Bioorg. Med. Chem. Lett.*, 30 (23) 127611.

12 Abdel-Mohsen S. A. (**2003**) Heterocycles Derived from 5-(2-Aminothiazol-4-yl)-8-hydroxyquinoline: Synthesis and Antimicrobial Activity. *J. Chin. Chem. Soc.*, 50 (5) 1085–1092.

13 Abdallah A. E. M., Mohareb R. M., Helal M. H. E., Mofeed G. J. (**2021**) Synthesis and Anticancer Evaluations of Novel Thiazole Derivatives Derived from 4-Phenylthiazol-2-Amine. *Acta Chim. Slov.*, 68 (3) 604–616.

14 Reddy V. R., Rao V. R. (**2005**) Synthesis of Some New 3-(2-Oxo-2*H*-chromen-3-yl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-ones. *Heterocyclic Commun.*, 11 (3-4) 299–304.

15 Ahmad N. M., Jones K. (**2010**) An Efficient Synthesis of Thiazolo[3,2-*a*]pyrimidinones. *Tetrahedron Lett.*, 51 (25) 3263–3265.

16 Peterlin-Mašič L., Malešič M., Breznik M., Krbavčič A. (**2000**) Synthesis of New Functionalized Imidazo[2,1-*b*]thiazoles and Thiazolo[3,2-*a*]pyrimidines. *J. Heterocyclic Chem*., 37 (1) 95–101.

17 Toche R. B., Ghotekar B. K., Kazi M. A., Kendre D. B., Jachak M. N. (**2007**) Synthesis of Fused Pyrimidines from Amines and Cyclic β-Formylesters. *Tetrahedron*, 63 (34) 8157–8163.

18 Zicane D., Ravinya I., Tetere Z., Rijkure I., Gudriniece E., Kalejs U. (**2000**) Exotic Amino Acids. 4. Synthesis of Methyl Esters of Some *N*-Heteroamino-Methylenemalonic Acids. *Chem. Heterocyclic Compd.*, 36 (6) 754–757.

19 Bonacorso H. G., Lourega R. V., Wastowski A. D., Flores A. F. C., Zanatta N., Martins M. A. P. (**2002**) β-Alkoxyvinyl Trichloromethyl Ketones as *N*-Heterocyclic Acylating Agent. A New Access to 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones. *Tetrahedron Lett.,* 43 (51) 9315–9318.

20 Campos P. T., Rodrigues L. V., Belladona A. L., Bender C. R., Bitencurt J. S., Rosa F. A., Back D. F., Bonacorso H. G., Zanatta N., Frizzo C. P., Martins M. A. P. (**2017**) Regiochemistry of Cyclocondensation Reactions in the Synthesis of Polyazaheterocycles. *Beilstein J. Org. Chem.*, 13 257–266.

21 El-Sayed R., Katouah H. A. (**2019**) Synthesis of Pyrimidine and Pyran Derivatives with the Related Systems and the Study of Their Behavior in the Liquid Solutions. *J. Heterocyclic Chem*., 56 (8) 2134–2143.

22 Jakše R., Svete J., Stanovnik B., Golobič A. (**2004**) Application of Alkyl 3-Dimethylamino-2-(1*H*-indol-3-yl)propenoates in the Synthesis of 3-Heteroarylindoles. *Tetrahedron*, 60 (21) 4601–4608.

23 Modranka J., Janecki T. (**2011**) Efficient Synthesis of Phosphorylated Ortho-Fused Azaheterocycles. *Tetrahedron*, 67 (49) 9595–9601.

24 Papadopoulos K., Young D. W. (**2002**) Versatile Synthesis of Ibotenic Acid Analogues with Potential for Activity at Glutamate Receptors by Use of a Homochiral β-Lactam Template in Our ‘Ring Switching’ Strategy. *Tetrahedron Lett.*, 43 (21) 3951–3955.

25 Hitchcock P. B., Papadopoulos K., Young D. W. (**2003**) β-Lactams as Versatile Synthons for Homochiral Ibotenate Analogues with Potential for Activity at Glutamate Receptors1. *Org. Biomol. Chem.*, 1 (15) 2670–2681.

26 Jukić L., Svete J., Stanovnik B. (**2001**) Reactions of Alkyl (*Z*)-2-[(*E*)-2-Cyano-2-(2-pyridinyl)ethenyl]amino-3-dimethylaminopropenoates with *C*- and *N*-Nucleophiles. The Synthesis of Fused 2*H*,5*H*-Pyran-2,5-diones, 4*H*-Pyrimidin-4-ones, and 1-Heteroaryl-1*H*-imidazole- 4-carboxylates. *Heterocycles*, 55 (4) 705–727.

27 Baš J., Recnik S., Svete J., Golic-Grdadolnik S., Stanovnik B. (**2001**) Synthesis and Transformations of Methyl (*Z*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(dimethylamino)propenoate. *Arkivoc*, 2001 (2) 61–68.

28 Bevk D., Kmetic M., Recnik S., Svete J., Golic L., Golobic A., Stanovnik B. (**2001**) Synthesis and Transformations of Ethyl (*Z*)-2-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)-3-(dimethylamino)propenoate. *Chem. Heterocyclic Comp.*, 37 (12) 1498–1510.

29 Japelj B., Rečnik S., Čebašek P., Stanovnik B., Svete J. (**2005**) Synthesis and Antimycobacterial Activity of Alkyl 1-Heteroaryl-1*H*-1,2,3-triazole-4-carboxylates. *J. Heterocyclic Chem.*, 42 (6) 1167–1173.

30 Čebašek P., Bevk D., Pirc S., Stanovnik B., Svete J. (**2006**) Parallel Synthesis of 3-Amino-4*H*-quinolizin-4-ones, Fused 3-Amino-4*H*-pyrimidin-4-ones, and Fused 3-Amino-2*H*-pyran-2-ones. *J. Comb. Chem.*, 8 (1) 95–102.

31 Erian A. W., Sherif S. M., Mohamed N. R. (**2003**) Heterocyclic Synthesis with Activated Nitriles: An Expeditious Synthetic Approach to Polyfunctionally Substituted Pyrroles, Heterocyclopyrimidines and Coumarins. *Synthetic Commun.*, 33 (9) 1563–1573.

32 Pandey S., Pandey P., Singh J. (**2014**) Synthesis, Characterization and Fungicidal Activity of *N*-(5-Oxo-3,7-diaryl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)benzamide Derivatives. *Der Pharma Chemica*, 6 (1) 170–175.

33 Bondock S., Fadaly W., Metwally M. A. (**2009**) Enaminonitrile in Heterocyclic Synthesis: Synthesis and Antimicrobial Evaluation of Some New Pyrazole, Isoxazole and Pyrimidine Derivatives Incorporating a Benzothiazole Moiety. *Eur. J. Med. Chem.*, 44 (12) 4813–4818.

34 El-Mekabaty A., M. O. Habib O. (**2018**) Efficient and Convenient Route to the Synthesis of Some Novel Sulfonate Ester-Based Heterocycles as Antitumor Agents. *Heterocycles*, 96 (4) 677–689.

35 El-Borai M. A., Rizk H. F., Ibrahim S. A., El-Sayed H. F. (**2017**) Microwave Assisted Synthesis of Fused Thiazoles in Multicomponent System and Their *in Vitro* Antitumor, Antioxidant, and Antimicrobial Activities. *J. Heterocyclic Chem.*, 54 (2) 1031–1041.

36 Pérez-Sánchez H., Den Haan H., Pérez-Garrido A., Peña-García J., Chakraborty S., Erdogan Orhan I., Senol Deniz F. S., Villalgordo J. M. (**2021**) Combined Structure and Ligand-Based Design of Selective Acetylcholinesterase Inhibitors. *J. Chem. Inf. Model.*, 61 (1) 467–480.

37 Zhong W., Guo B., Lin F., Liu Y., Su W. (**2009**) Regioselective Synthesis of 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones from Morita-Baylis-Hillman Adduct Acetates under Solvent-Free and Base-Free Conditions. *Synthesis*, 2009 (10) 1615–1622.

38 Liu Y., Wan K., Wang Z. (**2015**) Fast, Microwave-Promoted One-Pot Synthesis of Bicyclic Pyrimidones from Baylis-Hillman Adducts. *J. Chem. Res.*, 39 (2) 63–66.

39 Yadav L. D. S., Rai V. K., Yadav S. (**2006**) Novel Mercaptoacetylative Expeditious Annulation of 5-Mercaptopyrimidine Ring on Azoles Using 1,3-Oxathiolan-5-one. *Tetrahedron*, 62 (23) 5464–5468.

40 Lengyel L. C., Sipos G., Sipőcz T., Vágó T., Dormán G., Gerencsér J., Makara G., Darvas F. (**2015**) Synthesis of Condensed Heterocycles by the Gould–Jacobs Reaction in a Novel Three-Mode Pyrolysis Reactor. *Org. Process Res. Dev.*, 19 (3) 399–409.

41 Tsoung J., Bogdan A. R., Kantor S., Wang Y., Charaschanya M., Djuric S. W. (**2017**) Synthesis of Fused Pyrimidinone and Quinolone Derivatives in an Automated High-Temperature and High-Pressure Flow Reactor. *J. Org. Chem.*, 82 (2) 1073–1084.

42 Gupta R., Sharma D., Verma P. S., Jain A. (**2016**) Insecticidal Evaluation and [4+2] Aza-Diels-Alder Synthesis of 3,7-Diaryl-6,7-dihydro-5*H*-6-substituted Thiazolo[3,2-*a*]pyrimidin-5-ones Under Coupled Ultrasonic Irradiation and PTC. *J. Heterocyclic Chem.*, 53 (1) 38–45.

43 Yadav A. K., Sharma G. R., Dhakad P., Yadav T. A (**2012**) Novel Ionic Liquid Mediated Synthesis of 4(1*H*)-Quinolones, 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-one and 4*H*-Pyrimido[2,1-*b*]benzothiazol-4-ones. *Tetrahedron Lett.*, 53 (7) 859–862.

44 Devineni S. R., Madduri T. R., Chamarthi N. R., Liu C.-Q., Pavuluri C. M. (**2019**) An Efficient Microwave-Promoted Three-Component Synthesis of Thiazolo[3,2-*a*]pyrimidines Catalyzed by SiO_2–$ZnBr_2$ and Antimicrobial Activity Evaluation. *Chem. Heterocyclic Comp*., 55 (3), 266–274.

45 Deng Q.-G., Gao Y., Zhao B., Jiang L.-L., Liu Z., Song B. (**2013**) A Microwave Assisted Synthesis of Highly Substituted 7-Methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate Derivatives via One-Pot Reaction of Aminothiazole, Aldehyde and Ethyl Acetoacetate. *Hetercycles*, 87 (10) 2093–2102.

46 Batool I., Saeed A., Qureshi I. Z., Kalsoom S., Razzaq A. (**2016**) Synthesis, Molecular Docking and Biological Evaluation of New Thiazolopyrimidine Carboxylates as Potential Antidiabetic and Antibacterial Agents. *Res. Chem. Intermed*., 42 (2) 1139–1163.

47 Yadav L. D. S., Dubey S., Yadav B. S. (**2003**) Solvent-Free One-Pot Reactions for Annulating a Pyrimidine Ring on Thiazoles under Microwave Irradiation. *Tetrahedron*, 59 (29) 5411–5415.

48 Adib M., Nosrati M., Mahdavi M., Zhu L.-G., Mirzaei P. (**2007**) A Novel, One-Pot, Three-Component Synthesis of 5*H*-[1,3]Thiazolo[3,2-*a*]pyrimidine Derivatives. *Synlett*, 2007 (17) 2703–2706.

49 Kuai C., Teng B., Wu X. (**2024**) Palladium-Catalyzed Carbonylative Multicomponent Fluoroalkylation of 1,3-Enynes: Concise Construction of Diverse Cyclic Compounds. *Angew. Chem. Int. Ed*., 63 (8) e202318257.

50 Huang X., Liu Z. (**2002**) Solid-Phase Synthesis of 4(1*H*)-Quinolone and Pyrimidine Derivatives Based on a New ScaffoldPolymer-Bound Cyclic Malonic Acid Ester. *J. Org. Chem.*, 67 (19) 6731–6737.

51 Čebašek P., Wagger J., Bevk D., Jakše R., Svete J., Stanovnik B. (**2004**) Parallel Solution-Phase Synthesis of (*Z*)-3-(Arylamino)-2,3-Dehydroalanine Derivatives and Solid-Phase Synthesis of Fused Pyrimidones. *J. Comb. Chem.*, 6 (3) 356–362.

52 Fatima S., Sharma A., Sharma R., Tripathi R. P. A (**2012**) Simple and Efficient One-Pot Synthesis of Multifunctional 5-Aryl-*5H*-thiazolo[3,2-*a*]pyrimidines. *J. Heterocyclic Chem*., 49 (3) 600–606.

53 Castagnolo D., Pagano M., Bernardini M., Botta M. (**2009**) Domino Alkylation-Cyclization Reaction of Propargyl Bromides with Thioureas/Thiopyrimidinones: A New Facile Synthesis of 2-Aminothiazoles and 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones. *Synlett*, 2009 (13) 2093–2096.

54 Valasani K. R., Vangavaragu J. R., Day V. W., Yan S. S. (**2014**) Structure Based Design, Synthesis, Pharmacophore Modeling, Virtual Screening, and Molecular Docking Studies for Identification of Novel Cyclophilin D Inhibitors. *J. Chem. Inf. Model.*, 54 (3) 902–912.

55 Okamoto S., Sakai Y., Watanabe S., Nishi S., Yoneyama A., Katsumata H., Kosaki Y., Sato R., Shiratori M., Shibuno M., Shishido T. (**2014**) Structure–Activity Relationship of Dihydroimidazo-, Dihydropyrimido-, Tetrahydrodiazepino[2,1-*b*]thiazoles, and -Benzothiazoles as an Acylation Catalyst. *Tetrahedron Lett.*, 55 (11) 1909–1912.

56 Lecat-Guillet N., Ambroise Y. (**2009**) Synthesis and Evaluation of Imidazo[2,1-*b*]thiazoles as Iodide Efflux Inhibitors in Thyrocytes. *ChemMedChem*, 4 (11) 1819–1830.

57 Ochiai M., Nishi Y., Hashimoto S., Tsuchimoto Y. Chen D.-W. (**2003**) Synthesis of 2,4-Disubstituted Thiazoles from (*Z*)-(2-Acetoxyvinyl)Phenyl-λ^3-Iodanes: Nucleophilic Substitution of α-λ^3-Iodanyl Ketones with Thioureas and Thioamides. *J. Org. Chem.*, 68 (20) 7887–7888.

58 Pivazyan V. A., Ghazaryan E. A., Shainova R. S., Tamazyan R. A., Ayvazyan A. G., Yengoyan A. P. (**2017**) Synthesis and Growth Stimulant Properties of 2-Acetyl-3,7-dimethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one Derivatives. *J. Chem.*, 2017 1–8.

59 Mohamed S. F., Flefel E. M., Amr A. E.-G. E., Abd El-Shafy D. N. (**2010**) Anti-HSV-1 Activity and Mechanism of Action of Some New Synthesized Substituted Pyrimidine, Thiopyrimidine and Thiazolopyrimidine Derivatives. *Eur. J. Med. Chem.*, 45 (4) 1494–1501.

60 Youssef M. M., Youssef A. M. S. (**2003**) Reactions with 2-Thiothymine; Selective Cyclization of S-Substituted 2-Thiothymine. *Phosphorus, Sulfur, and Silicon and the Related Elements*, 178 (1) 67–81.

61 Bakavoli M., Mollashahi E., Seyedi S. M., Rahimizadeh M. (**2007**) Synthesis of New Thiazolo[3,2-*a*:4,5-*d*]dipyrimidine Derivatives. *Heterocyclic Commun.*, 13 (5) 283–288.

62 Selvam T. P., Karthik V., Kumar P. V., Ali M. A. (**2012**) Design, Synthesis, Antinociceptive, and Anti-Inflammatory Properties of Thiazolopyrimidine Derivatives. *Toxicological & Environmental Chem.*, 94 (7) 1247–1258.

63 Urbano M., Guerrero M., Velaparthi S., Crisp M., Chase P., Hodder P., Schaeffer M.-T., Brown S., Rosen H., Roberts E. (**2011**) Discovery, Synthesis and SAR Analysis of Novel Selective Small Molecule S1P4-R Agonists Based on a (2*Z*,5*Z*)-5-[(Pyrrol-3-yl)Methylene]-3-alkyl-2-(alkylimino)thiazolidin-4-one Chemotype. *Bioorg. Med.l Chem. Lett.*, 21 (22) 6739–6745.

64 Abdel Moty S. G., Hussein M. A., Abdel Aziz S. A., Abou-Salim M. A. (**2016**) Design and Synthesis of Some Substituted Thiazolo[3,2-*a*]pyrimidine Derivatives of Potential Biological Activities. *Saudi Pharm. J.*, 24 (2) 119–132.

65 Keshari M., Khan R. A., Khalilullah H., Yusuf M., Ahmed B. (**2020**) Pharmacophore Modeling, Design, and Synthesis of Potent Antihypertensives, Oxazolo/Thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one, and 1,5-Dihydroimidazo[1,2-*a*]pyrimidin-3(2*H*)-one Derivatives: A Pilot Trial. *Bioorg. Med. Chem. Lett.*, 30 (23), 127604.

66 Jin C.-H., Jun K.-Y., Lee E., Kim S., Kwon Y., Kim K., Na Y. (**2014**) Ethyl 2-(Benzylidene)-7-methyl-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate Analogues as a New Scaffold for Protein Kinase Casein Kinase 2 Inhibitor. *Bioorg. Med. Chem.*, 22 (17) 4553–4565.

67 Bhalgat C. M., Ramesh B. (**2014**) Synthesis, Antimicrobial Screening and Structure–Activity Relationship of Novel Pyrimidines and Their Thioethers. *Bull. Faculty Pharm. Cairo Univ.*, 52 (2), 259–267.

68 Mugnaini C., Manetti F., Esté J. A., Clotet-Codina I., Maga G., Cancio R., Botta M., Corelli F. (**2006**) Synthesis and Biological Investigation of *S*-Aryl-*S*-DABO Derivatives as HIV-1 Inhibitors. *Bioorg. Med. Chem. Lett.*, 16 (13) 3541–3544.

69 Shajari N., Ghiasi R., Ramazani A. (**2023**) Experimental and Computational Insights for Identification of Dialkyl 5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3-dicarboxylates. *Chem. Rev. Lett.*, 6 (1) 24–28.

70 Yang Z., Liu S., Li A., Liao J., Li L., Yang T., Zhou C. (**2019**) KI/$K_2S_2O_8$-Mediated C-S/C-N Bond Formation: One-Pot Regioselective Synthesis of 5*H*-Thiazolo[3,2-*a*]pyrimidines. *ChemistrySelect*, 4 (21) 6583–6586.

71 Rognan C., Locquet P., Pertschi R., Girard N., Gulea M. (**2024**) Domino Doyle-Kirmse/Claisen-Thioimidate Rearrangements: Access to 2-Aminobuta-1,3-diene Derivatives of Benzazole-2-thiones. *Adv. Synth. Catal.*, 366 (19) 4078–4083.

72 Daghlavi A., Kowsari E., Abdouss M., Ghasemi M. H., Asadi E. (**2020**) Catalytic Synthesis of Thiazolidines by the Reaction of Nef-Isocyanide Reaction. *Res. Chem. Intermed.*, 46 (7) 3593–3605.

73 Attanasi O. A., De Crescentini L., Favi G., Filippone P., Giorgi G., Mantellini F., Perrulli F. R., Spinelli D. (**2008**) Simple Construction of Fused and Spiro Nitrogen/Sulfur Containing Heterocycles by Addition of Thioamides or Thioureas on Cycloalkenyl-Diazenes: Examples of Click Chemistry. *Tetrahedron*, 64 (17) 3837–3858.

74 Keivanloo A., Bakherad M., Shahani T., Amin A. H. (**2016**) Pd-Catalyzed Coupling Reaction of 6-Hydroxy-2-(prop-2-yn-1-ylsulfanyl)pyrimidin-4(1*H*)-one with Aryl Iodides: Efficient Syntheses of New 3-Benzylthiazolo[3,2-*a*]pyrimidinones. *Chem. Heterocyclic Comp.*, 52 (10) 836–839.

75 Mohlala R. L., Coyanis E. M., Fish M. Q., Fernandes M. A., Bode M. L. (**2021**) Synthesis of 6-Membered-Ring Fused Thiazine-Dicarboxylates and Thiazole-Pyrimidines via One-Pot Three-Component Reactions. *Molecules*, 26 (18) 5493.

76 Lei X., Wang Y., Fan E., Sun Z. (**2019**) *In Situ* Activation of Disulfides for Multicomponent Reactions with Isocyanides and a Broad Range of Nucleophiles. *Org. Lett.*, 21 (5) 1484–1487.

77 Yaremenko F., Beryozkina T., Khvat A., Svidlo I., Shishkin O., Shishkina S., Orlov V. (**2008**) 5,7-Substituted Thiazolo[2,3-*a*]pyrimidines: Synthesis, Stereochemistry and Crystal Structure. *J. Mol. Structure*, 874 (1-3) 57–63.

78 C. Liotta D., B. Ambhaikar N., Herold M. A (**2004**) Uniquely Accessible Route to the Diastereoselective Synthesis of Azetine Derivatives. *Heterocycles*, 62 (1) 217–222.

79 MacNevin C. J., Moore R. L., Liotta D. C. (**2008**) Stereoselective Synthesis of Quaternary Center Bearing Azetines and Their β-Amino Acid Derivatives. *J. Org. Chem.*, 73 (4) 1264–1269.

80 Aretz J., Anumala U. R., Fuchsberger F. F., Molavi N., Ziebart N., Zhang H., Nazaré M., Rademacher C. (**2018**) Allosteric Inhibition of a Mammalian Lectin. *J. Am. Chem. Soc.*, 140 (44) 14915–14925.

81 Thoma G., Streiff M. B., Kovarik J., Glickman F., Wagner T., Beerli C., Zerwes H.-G. (**2008**) Orally Bioavailable Isothioureas Block Function of the Chemokine Receptor CXCR4 *In Vitro* and *In Vivo*. *J. Med. Chem.*, 51 (24) 7915–7920.